

EXHIBIT 22

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER
PRODUCTS MARKETING, SALES PRACTICES, AND
PRODUCTS LIABILITY LITIGATION

STEVEN J. KIM, INDIVIDUALLY AND O/B/O THE
ESTATE OF LYNDIA BONDURANT,

Plaintiffs,

v.

JOHNSON & JOHNSON, et al.,


Defendants.

MDL NO. 16-2738 (FLW) (LHG)

Civil Action No. 3:19-cv-14366-FLW-LHG

EXPERT REPORT OF MICHAEL A. FINAN, M.D.

Date: May 28, 2024



Michael A. Finan, M.D.

SCOPE OF REPORT

I was asked to render an opinion as to whether talcum powder can cause or contribute to the development of ovarian cancer in general, and specifically, whether it did so with regards to Linda Bondurant. My opinions are based on my education, training, and 30 years of medical practice as a board-certified obstetrician gynecologist and gynecologic oncologist, as well as a review of pertinent literature, and relevant statements of national and international organizations, medical records, and deposition testimony.

I hold all the opinions in this report to a reasonable degree of medical certainty. I am being compensated at a rate of \$650.00 per hour for my time spent away from my practice and my family, and for my efforts in providing this expert opinion.

PERSONAL BACKGROUND

I have a full-time medical practice dedicated to gynecologic oncology. I serve as Chief of Oncology Services, as well as Chief of Women's Services, for the Singing River Health System on the Gulf Coast of Mississippi. I grew up in New Orleans and completed undergraduate education at the University of New Orleans, after which I was accepted at LSU Medical School Shreveport. As a 3rd year medical student, I chose to dedicate my medical career to women's health by choosing Obstetrics and Gynecology as my field of study for residency training. I graduated from Louisiana State University Health Sciences Center, Shreveport, Louisiana in 1986. My residency in Obstetrics and Gynecology was completed in 1990 at the University of South Florida in Tampa, and at Tampa General Hospital. I received several teaching awards during my Obstetrics and Gynecology residency training, but the most prestigious award was being elected to the National AOA Honor Society by the medical students whom I taught. During my residency, I was drawn to caring for women with gynecologic cancers. In my third year of Obstetrics and Gynecology residency, I applied for and was accepted into Gynecologic Oncology fellowship training at the University of South Florida, with clinical training at the H. Lee Moffitt Cancer Center and Tampa General Hospital. The H. Lee Moffitt Cancer Center is one of the approximately 60 NCI Designated Comprehensive Cancer Centers in the United States. Other NCI Comprehensive Cancer Centers include MD Anderson, Memorial Sloan Kettering, and Johns Hopkins. My fellowship training extended from 1990 – 1992. Both residency and fellowship training require research as a component, with more formal training in research during the fellowship, including two graduate-level courses in statistics. Additionally, application of the principles of epidemiology is a critical component of both residency and fellowship training, the details of which can be found at acgme.org (Accreditation Council for Graduate Medical Education).

In 1992, I joined the staff at Ochsner Clinic in New Orleans as a Gynecologic Oncologist. My role there involved clinical duties, which included seeing approximately 30-35 patients per day in clinic and performing approximately 8-12 operations per week from 1992-2005. During this time, I was awarded the resident teaching award several times, including the national CREOG Teaching Award (Council for Resident Education in Obstetrics and Gynecology). My role expanded to include directing resident research projects, in addition to my own clinical research, which eventually led to serving as the Obstetrics and Gynecology Residency Program Director. As Residency Program Director, I was deeply involved and solely responsible for maintaining the accreditation of the Obstetrics and Gynecology Residency Program. It was critical for me to understand and implement the training and teaching guidelines of the ACGME as well as CREOG (creog.org). While serving at Ochsner, I was named to

several national lists of Best Physicians, Top Doctors, as well as Best Gynecologic Oncologist (U.S. News and World Report, Ladies Home Journal, Castle Connolly).

I was recruited to Mobile, Alabama in July 2005 as a Professor of Gynecologic Oncology to the University of South Alabama (USA). The Mitchell Cancer Institute was constructed in 2007, at which time I joined the USA Mitchell Cancer Institute. My role there included the three-part mission of an Academic Cancer Center: clinical care, education, and research. Specifically, I continued to see approximately 30-35 patients one day per week in clinic and to perform 8-12 operations per week on average. Approximately 30% of my practice was and continues to be benign gynecology. These included prophylactic surgeries for women at high risk for gynecologic malignancy, technically difficult cases, or cases in which the referring physician was uncomfortable managing the problem. My referral base extended in an arc across the Gulf Coast from the Alabama-Georgia border to the east, and to the Mississippi-Louisiana line to the west. My teaching duties included teaching medical students, residents, and hematology-oncology fellows. These teaching duties have included teaching on rounds, in clinic, in the operating room, as well as via lectures and grand rounds. I have been awarded many teaching awards while serving at the USA Mitchell Cancer Institute, both departmental awards, as well as the national CREOG Teaching Award. While serving at the USA Mitchell Cancer Institute, I continued to be named to several national lists of Best Physicians, Top Doctors as well as Best Gynecologic Oncologist (U.S. News and World Report, CastleConnolly, etc.).

My research has included both clinical research as well as translational science (bench to bedside research), as well as collaborating on a few basic science projects. Most significant has been my research into a potential screening test for the early detection of ovarian cancer. This project began in 2008 in collaboration with my associates. We initially came up with the idea to potentially screen for endometrial cancer (cancer of the uterine body) using pap smear fluid. It is important to note that there are only a handful of cancers that we can currently screen for, resulting in early detection, lives saved and reduced mortality: cervix (pap), breast (mammogram), colon (colonoscopy or Cologuard, FIT test), prostate (PSA), lung (low dose CT scan) and melanoma (skin exams). For the remaining nearly hundred other cancers, including ovarian and uterine, there are no effective screening tests. Our idea, which resulted in the filing of six patents, was to take fluid from a pap test and analyze the protein profile. Pap tests are performed by inserting a speculum in the vaginal vault to open the vagina to visualize the cervix. Once visualized, a specimen is taken with a cyto-brush inserted into the cervical os to obtain endocervical cells. As a result of using the cyto-brush, a specimen of endocervical mucus is obtained, which contains the cells of interest for a pap test. For decades, the fluid has been sent to cytopathologists, who then inspect the cells, discarding the fluid as biomedical waste. We decided to spin down the fluid and discard or biobank the cells and analyze the acellular pap fluid. The acellular pap fluid contains a rich repository of mucus and proteins/peptides, which were of interest to our research. Specifically, we were interested in the peptide "fingerprint" unique to each patient. Our research initially was focused on cancers of the uterine body, but we quickly shifted our focus to the early detection of ovarian cancer. The anatomy and function of the female reproductive system and genital tract is such that the ovaries are always bathed in a proteinaceous fluid. The fallopian tubes ostia rest immediately adjacent to the respective ovaries. The entire function of the fallopian tubes is to transport eggs, in this proteinaceous fluid, from the ovary to the endometrial cavity (uterine lining) where they would be potentially fertilized and implanted as an embryo. The proteinaceous fluid, which had bathed the ovaries, then flows very slowly out of the endocervical os along with the cervical mucus. Our hypothesis in 2008 was that if we obtained specimens of endocervical mucus, they might contain a unique fingerprint of peptides, allowing us to differentiate early-stage ovarian cancer from controls.

Our findings were published in the peer-reviewed journal *Gynecologic Oncology* in November 2021.¹ We applied for a peer-reviewed, federally funded grant called an R-01 grant in 2012 (1 R01 CA164940-01A1) and received approximately 1.3 million dollars in funding to study our methods. We partnered with approximately 20 sites across the United States. These 20 sites, including the USA Mitchell Cancer Institute, enrolled patients and collected specimens over an approximately 4-year period. Our hypothesis was ultimately confirmed, and we demonstrated that a unique protein/peptide fingerprint identifies patients with early-stage (stages 1 & 2) ovarian cancer when compared to controls. The reason this is pertinent is that the direction of the flow of this proteinaceous fluid is from the ovary, through the fallopian tube, through the endometrial cavity and out through the cervical os.

In October 2014, I was asked to serve as Cancer Center Director for the USA Mitchell Cancer Institute. My leadership role responsibilities included strategic planning, basic and translational research, clinical research, faculty development, faculty recruiting, human resources, and the myriad other responsibilities that come with leading an academic cancer center. During my time as Cancer Center Director, I did continue to see patients, perform surgery, administer chemotherapy, and the many other activities of a gynecologic oncologist. My roles in this position were about 80% administrative and 20% clinical. During this time, I also served on the University President's Council, which served essentially as the University President's Cabinet. As I neared retirement, after more than four years in this role, I chose to step down in December 2018, in order to move back into a clinical position, caring for gynecologic cancer patients, which has always been my passion.

I retired from the University of South Alabama on April 1, 2020, and was recruited to serve as Chief of Cancer Services, as well as Chief of Women's Services, for the Singing River Health System on the Gulf Coast of Mississippi. My role as Chief of Cancer Services is an administrative role with somewhat similar responsibilities as those that I held at the MCI, including overseeing clinical research. I also oversee the Cancer Risk Assessment (CRA) program for our health system. The CRA assesses risk based on family history for every woman undergoing a mammogram at Singing River. Based on this family history, women at increased risk are offered genetic testing and more intense screening based on a scoring system. I have also continued my clinical practice of Gynecologic Oncology, serving the patients in the referral zone described above in my new practice. I see approximately 25-30 patients per week in clinic and perform 6-8 surgical procedures per week on average. My role in this position is about 80% clinical and 20% administrative.

SUMMARY OF OPINIONS

- The application of talcum powder, regardless of its constituents, to the female perineum does not cause or contribute to the development of ovarian cancer.
- Other than germline genetic mutations (e.g., BRCA, Lynch syndrome and other mutations) which are known genetic causes of ovarian cancer, most ovarian cancers are sporadic and have no identifiable or known cause. That said, there are established risk factors that are outlined by

¹ Rocconi, R. P., Wilhite, A. M., Schambeau, L., Scalici, J., Pannell, L., & Finan, M. A. (2021). A novel proteomic-based screening method for ovarian cancer using cervicovaginal fluids: A window into the abdomen. *Gynecologic Oncology*. Advance online publication. <https://doi.org/10.1016/j.ygyno.2021.10.083>.

major national organizations and societies in the United States that gynecologic oncologists and patients rely on for information about ovarian cancer.

- These organizations include the National Institutes of Health-National Cancer Institute (NIH-NCI)², the Society of Gynecologic Oncology (SGO)³, the American College of Obstetricians and Gynecologists (ACOG)⁴, United States Food & Drug Administration⁵, the National Comprehensive Cancer Network (NCCN)⁶, American Cancer Society (ACS)⁷ and the United States Centers for Disease Control and Prevention (CDC)⁸. None of these organizations lists talcum powder as a risk factor for ovarian cancer.
- The female reproductive system is not an open system, and has several anatomic and physiologic barriers to protect it from exposure to foreign elements.
- There are no studies that demonstrate that talcum powder, applied as a dusting to the female perineum, can migrate upwards through the female genital tract and reach the fallopian tubes or ovaries.
- Inflammation does not cause ovarian cancer.
- In high-risk patients who have prophylactic surgery, and are found to have precursor STIC lesions, there is no associated inflammation found on histology.
- The literature does not show a consistent increased risk of ovarian cancer from inflammatory diseases, such as PID.
- The literature does not consistently demonstrate a reduction in risk of ovarian cancer from NSAIDs or aspirin, and gynecologic oncologists do not counsel women to take such anti-inflammatory medications to reduce their risk.
- There are no studies that demonstrate that talcum powder applied to benign ovarian cells can transform these benign ovarian cells into malignant ovarian cancer cells.
- Linda Bondurant's use of talcum powder did not cause or contribute to the development of her ovarian cancer.

² National Cancer Institute, *Ovarian, Fallopian Tube and Primary Peritoneal Cancer Prevention (PDQ): Who is at Risk?* (updated March 6, 2024).

³ Society of Gynecologic Oncology. *Ovarian Cancer Risk Factors*. Retrieved March 7, 2024, from <https://www.sgo.org/patients-caregivers-survivors/caregivers/ovarian-cancer-risk-factors/>.

⁴ American College of College of Obstetrics and Gynecologists: *Frequently Asked Questions Gynecologic Problems. Ovarian Cancer FAQ096*. Published April 2019; Last Updated May 2022. <https://www.acog.org/Patients/FAQs/Ovarian-Cancer>.

⁵ Food and Drug Administration Letter from Musser SM to Epstein SS Re: Docket Numbers 94P-0420 and FDA-2008-P-0309-0001/CP. Date stamped: April 1, 2014. FDA Denial of 1994 and 2008 Petitions.

⁶ National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer. Version 1.2024.

⁷ American Cancer Society. (2024). Cancer Facts & Figures 2024. *American Cancer Society*.

⁸ Centers for Disease Control and Prevention. *What are the Risk Factors for Ovarian Cancer?* (June 14, 2023) https://www.cdc.gov/cancer/ovarian/basic_info/risk_factors.htm.

OVARIAN CANCER BACKGROUND

Ovarian cancer affects about 20,000 women per year in the United States, with about 14,000 deaths each year.⁹ The incidence and death rate have remained fairly consistent for nearly the past 100 years for which we have data. Ovarian cancer is relatively rare, with a lifetime risk of about 1.2%, according to the SEER database.¹⁰ Cancers that are more common in women annually in the United States than ovarian include: breast (310,000 annually), GI (colon, rectal, and other cancers of the gastrointestinal tract, 156,000 annually), lung (118,000 annually), skin (44,000 annually), GU (cancers of the bladder and kidneys, 51,000 annually) and leukemia (26,000 annually).¹¹ With ovarian cancer incidence only involving about 20,000 women each year in the United States, it makes it more difficult to study in some cases.

Many different cells make up the ovary, but cancers of the ovary can generally be divided into 3 major groups based on the cell types: germ cell, sex-cord stromal cell, and epithelial cell. Epithelial ovarian cancer is by far the most deadly and accounts for about 90% of ovarian cancer cases. Epithelial ovarian cancer is the focus of this report. The majority of women with ovarian cancer, about 75%, present initially with advanced disease (either Stage III or Stage IV). The majority present with gastro-intestinal symptoms including abdominal bloating, swelling, early satiety (feeling full after only a few bites of food), fatigue, pelvic pressure, urinary frequency and urgency, as well as other symptoms. When diagnosed early, such as Stages I-II, the cure rate can be as high as 80-90%. However, the overall cure rate with advanced disease remains low with an approximate 30-40% 5-year survival.

EPITHELIAL OVARIAN CANCER

Within the general category of epithelial ovarian cancer, there are several subtypes, including: endometrioid, high grade serous, low grade serous, mucinous, and clear cell, making up the vast majority in the epithelial cell group. These epithelial ovarian cancer subtypes can be divided into two categories, Type 1 and Type II tumors. Type 1 tumors are comprised of three groups (1) endometriosis-related tumors, which include endometrioid, clear cell, and sero-mucinous carcinomas; (2) low-grade serous carcinomas; and (3) mucinous carcinomas and malignant Brenner tumors. Type II tumors are comprised of high-grade serous carcinomas, high grade endometrioid carcinoma, and carcinosarcomas.^{12,13} These cell types are based on what the tumor looks like under a microscope. Each cell type has specific molecular genetic features and risk factors. When one looks at the molecular makeup

⁹ National Cancer Institute, Surveillance, Epidemiology and End Results Program: Cancer Stat Facts: Ovarian Cancer Retrieved January 18, 2024 from <https://seer.cancer.gov/statfacts/html/ovary.html>.

¹⁰ National Cancer Institute, Surveillance, Epidemiology and End Results Program: Cancer Stat Facts: Ovarian Cancer Retrieved January 18, 2024 from <https://seer.cancer.gov/statfacts/html/ovary.html>

¹¹ American Cancer Society. (2024). Cancer Facts & Figures 2024. American Cancer Society.

¹² Kurman, R. J., & Shih, I. M. (2016). The dualistic model of ovarian carcinogenesis: revisited, revised, and expanded. *The American Journal of Pathology*, 186(4), 733-747.

¹³ Dion, L., Carton, I., Jaillard, S., Nyangoh Timoh, K., Henno, S., Sardain, H., ... & Lavoué, V. (2020). The Landscape and Therapeutic Implications of Molecular Profiles in Epithelial Ovarian Cancer. *Journal of Clinical Medicine*, 9(7), 2239.

of these tumors, there are dozens, if not hundreds, of genetic and molecular features that distinguish one patient's tumor from the next. This biologic diversity is true even among women who have the same general cell type as seen under the microscope (i.e., serous). Some of the features of these groups are generally unique to the group. For example, endometrioid and clear cell ovarian cancers are generally thought to arise within areas of endometriosis.¹⁴ Serous (a.k.a. papillary serous) tumors are thought to arise generally from cells in the distal portion (the segment closest to the ovary) of the fallopian tube. High-grade serous cancers of the ovary derive from a precursor lesion in the fallopian tube called Serous Tubal Intraepithelial Carcinoma ("STIC").

RISK FACTORS FOR OVARIAN CANCER

We cannot determine the cause of most cancers. In fact, we do not know the cause of cancers of the breast, prostate, kidney, colon or most other cancers. Risk factors are, more often than not, just that. They are not causative in most cases, but simply put patients at "increased risk." Risk factors for ovarian cancer can be broken down into several groups, including:

- Genetics/Family History
- Environmental
- Reproductive
- Other

Genetics/Family History

Overall, about 30% of women with serous ovarian cancer have a known genetic mutation as the etiology.¹⁵ The majority of these pathologic genetic mutations are due to BRCA 1 and 2 mutations, 1% due to the Lynch syndrome mismatch repair genes (MSH2, MLH1, MSH6 AND PMS2) and the remainder due to a variety of other mutations. Additional genetic mutations continue to be identified, with more than 2 dozen reported mutations related to ovarian cancer having been identified to date. Variants of unknown significance (VUS) are commonly found to be associated with diseases as further testing is refined over time. Genetic counseling and genetic testing are recommended for all patients diagnosed with epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer.

When a patient presents with a family history of ovarian or breast cancer, or if a woman presents with either of these at a young age (<50), genetic counseling and genetic testing are recommended.¹⁶ It is important to point out that genetic testing is constantly being developed, expanded, and updated. We do not have the ability to rule out a genetic cause in cases where one is suspected. There are many women

¹⁴ Saavalainen, L., Lassus, H., But, A., Tiitinen, A., Härkki, P., Gissler, M., ... & Heikinheimo, O. (2018). Risk of gynecologic cancer according to the type of endometriosis. *Obstetrics & Gynecology*, 131(6), 1095-1102.

¹⁵ Kurian, A. W., Ward, K. C., Howlader, N., Deapen, D., Hamilton, A. S., Mariotto, A., ... & Katz, S. J. (2019). Genetic testing and results in a population-based cohort of breast cancer patients and ovarian cancer patients. *Journal of Clinical Oncology*, 37(15), 1305-1315.

¹⁶ National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. *Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer*. Version 1.2024.

with a strong family history of either breast and/or ovarian cancer who have a negative genetic test but are still at increased risk of developing ovarian cancer. With a first-degree relative having ovarian cancer, the lifetime risk to the patient increases from a baseline risk of 1.5% to 5-7% lifetime risk. This increase in risk is independent of any genetic testing results. A positive genetic test specifies its associated lifetime risk. With only approximately 30% of cases being related to germline mutations, the remainder (70%) are referred to as sporadic (random). In other words, outside of germline genetic mutations, we do not know the cause of the remaining 70% of ovarian cancers.

Environmental

Tobacco

Cigarette smoking has been shown to be a risk factor for the development of mucinous ovarian cancer, but not other cell types of ovarian cancer. There is a dose-response relationship with smoking in that the higher the pack-year exposure, the higher the risk of mucinous ovarian cancer.¹⁷

¹⁷ Jordan, S. J., Whiteman, D. C., Purdie, D. M., Green, A. C., & Webb, P. M. (2006). Does smoking increase risk of ovarian cancer? A systematic review. *Gynecologic Oncology*, 103(3), 1122-1129.

Reproductive

Pregnancy

Pregnancy has a protective effect with regard to ovarian cancer, which is additive. In other words, the more times a woman is pregnant, the lower her risk of ovarian cancer.

Breast Feeding

Breastfeeding is associated with a risk reduction of about 20-25%. The protective effect is additive in that the longer a woman breastfeeds, the lower her risk of developing ovarian cancer. There is a biologic gradient with regard to the protective effect of breastfeeding with ≤ 6 mos resulting in a 15% reduction in risk, 6-12 in a 27% reduction, and >12 resulting in a 36% reduction.¹⁸

Early Menarche and Late Menopause

Early menarche (first menses) and late menopause are associated with an increased risk of ovarian cancer.

Infertility

A history of infertility is associated with an increased risk of ovarian cancer. This increased risk is independent of whether fertility agents were used or not.

Tubal Ligation

Tubal ligation is associated with a decreased risk of ovarian cancer. The mechanism of action related to bilateral tubal ligation (BTL) and risk reduction of ovarian cancer is unclear. BTL is associated with significant acute inflammation when it is performed, and this inflammation may result in a protective effect described as quiescence.¹⁹

Oral Contraceptive Pills

Oral contraceptive pills (OCPs) have a protective effect and are associated with a decreased risk of ovarian cancer. In fact, if a woman takes OCPs for five years or more, her risk can be cut by as much as 50%. There is no other medical intervention (pill or other medicine) that can reduce a woman's risk of ovarian cancer like OCPs. When one reviews the public statements of national health care organizations such as ACOG, CDC, SGO, and NIH, all of them are in agreement that OCPs taken for 5 years or more reduce the risk of ovarian cancer.

¹⁸ Li, D. P., Du, C., Zhang, Z. M., Li, G. X., Yu, Z. F., Wang, X., ... & Zhao, Y. S. (2014). Breastfeeding and ovarian cancer risk: a systematic review and meta-analysis of 40 epidemiological studies. *Asian Pacific Journal of Cancer Prevention*, 15(12), 4829-4837.

¹⁹ Tiourin, E., Velasco, V. S., Rosales, M. A., Sullivan, P. S., Janzen, D. M., & Memarzadeh, S. (2015). Tubal ligation induces quiescence in the epithelia of the fallopian tube fimbria. *Reproductive Sciences*, 22(10), 1262-1271.

Endometriosis

Endometriosis increases a woman's risk of developing ovarian cancer 2-3 fold. The association is stronger with non-serous histologic subtypes. Specifically, clear cell ovarian cancer and endometrioid ovarian cancer cell types are associated with endometriosis, with clear cell accounting for 16.3% (21/129) and endometrioid accounting for 25.5% (33/129) of endometriosis-associated ovarian cancers.²⁰ A population-based study of women with surgically verified endometriosis by Saavalainen, et al. found that the risk of ovarian cancer was highest among women with ovarian endometriosis, especially with endometrioid (OR 4.72 [2.75-7.56]) and clear cell (OR 10.1 [5.50-16.9]) ovarian cancer.²¹ Phung et al. published an article in November 2022 with talc plaintiffs' expert Dr. Daniel Cramer as a co-author, which concluded that there is a greater risk of ovarian cancer with talc use in women with endometriosis versus without; however, this interaction was not statistically significant.²² The authors analyzed data from 9 population-based case-control studies, many of which I have reviewed in this expert report. Importantly, in the supplemental tables, the authors point out that talc use data were not available in more than 40% of cases. Additionally, the percentage of cases and controls with genital talc use was only about 9-11%.²³

Postmenopausal Hormone Replacement Therapy

The studies on hormone replacement therapy and risk of ovarian cancer have been inconsistent, as studies have reported on the health benefits and risks associated with its use. The Women's Health Initiative prospective cohort trial did not find an increase in risk with regard to hormone replacement therapy and ovarian cancer. They reported an O.R. of 1.6, CI 0.8-3.2 (42 versus 27 cases per 100,000 person-years), which is not statistically significant. The public statements of national health care organizations such as SGO and NIH state that women who are on estrogen replacement therapy only (without progesterone) for more than five years are considered at increased risk in the range of 20-40%.

Bilateral Salpingo-oophorectomy

Surgical removal of the tubes and ovaries offers a protective effect approaching 100%. There is a downside to removing the tubes and ovaries, particularly when they are removed prior to menopause. Increased risk of osteoporosis, cardiovascular disease, cerebrovascular accident (CVA or stroke), and death from all causes are increased in women who have a bilateral salpingo-oophorectomy.²⁴ This is particularly true when surgery occurs before menopause.

²⁰ Saavalainen, L., Lassus, H., But, A., Tiitinen, A., Härkki, P., Gissler, M., ... & Heikinheimo, O. (2018). Risk of gynecologic cancer according to the type of endometriosis. *Obstetrics & Gynecology*, 131(6), 1095-1102.

²¹ Saavalainen, L., Lassus, H., But, A., Tiitinen, A., Härkki, P., Gissler, M., ... & Heikinheimo, O. (2018). Risk of gynecologic cancer according to the type of endometriosis. *Obstetrics & Gynecology*, 131(6), 1095-1102.

²² Phung, MT et al. 2018. Effects of risk factors for ovarian cancer in women with and without endometriosis. *Fertil. Steril.*, 118(5):960-969.

²³ Phung, MT et al. 2018. Effects of risk factors for ovarian cancer in women with and without endometriosis. *Fertil. Steril.*, 118(5):960-969.

²⁴ Anderson, G. L., Judd, H. L., Kaunitz, A. M., Barad, D. H., Beresford, S. A., Pettinger, M., ... & Women's Health Initiative Investigators. (2003). Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA*, 290(13), 1739-1748.

Other

Age

The median age of diagnosis of ovarian cancer is 62. Thus, advancing age, particularly after the age of 60, is a risk factor for ovarian cancer. This is true for many cancers. As one ages, the overall risk of most cancers increases with each year of aging. Age does not cause ovarian cancer. The risk of ovarian cancer simply increases as a woman ages. A study by Tomasetti and Vogelstein (2017) found that two-thirds of cancer cases are due to random mistakes made during normal DNA replication. Accordingly, the longer a person lives, the more likely these mutations will occur and increase the chance of developing cancer, including ovarian cancer.²⁵

Obesity

In some studies, obesity has been found to increase the risk of ovarian cancer. Mortality is also worsened in many cases with obesity and ovarian cancer. Cell types particularly associated with obesity include mucinous, borderline, endometrioid, and clear cell carcinomas of the ovary. The risk of ovarian cancer increases as a woman's Body Mass Index (BMI) increases.

INTERNATIONAL & NATIONAL ORGANIZATIONS AND SOCIETIES

The major national organizations and societies in the United States do not list talcum powder as a risk factor for ovarian cancer. These include the National Institutes of Health-National Cancer Institute (NIH-NCI), the Society of Gynecologic Oncology (SGO), the American College of Obstetricians and Gynecologists (ACOG), and the United States Centers for Disease Control and Prevention (CDC).^{26,27,28,29} The SGO, ACOG, American Cancer Society (ACS) and the CDC all identify well established risk factors for ovarian cancer on their websites, and do not include talc or asbestos. ACOG also issued a statement that "There is no medical consensus that talcum powder causes ovarian cancer."³⁰ In fact, ACOG issued Committee Opinion #619 on "Gynecologic Surgery in the Obese Woman." In this committee opinion, ACOG recommends talc application as a modality to reduce postoperative wound complications in

²⁵ Tomasetti, C., Li, L., & Vogelstein, B. (2017). Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science*, 355(6331), 1330-1334.

²⁶ Society of Gynecologic Oncology. *Ovarian Cancer Risk Factors*. Retrieved March 7, 2024, from <https://www.sgo.org/patients-caregivers-survivors/caregivers/ovarian-cancer-risk-factors/>.

²⁷ American College of Obstetrics and Gynecologists: *Frequently Asked Questions Gynecologic Problems. Ovarian Cancer FAQ096*. Published April 2019; Last Updated May 2022. <https://www.acog.org/Patients/FAQs/Ovarian-Cancer>.

²⁸ National Cancer Institute, *Ovarian, Fallopian Tube and Primary Peritoneal Cancer Prevention (PDQ): Who is at Risk?* (updated October 16, 2023) https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq#cit/section_1.11.

²⁹ Centers for Disease Control and Prevention. *What are the Risk Factors for Ovarian Cancer?* (June 14, 2023) https://www.cdc.gov/cancer/ovarian/basic_info/risk_factors.htm.

³⁰ The American College of Obstetricians and Gynecologists.(2017, September 11). *Talc Use and Ovarian Cancer*. <https://www.acog.org/news/news-releases/2017/09/talc-use-and-ovarian-cancer>.

obese patients.³¹ The CDC similarly recommends using talc as a treatment for complications of genital warts after treatment with Trichloro-acetic acid.³² In 2023, the CDC funded ACOG to form an expert review panel that included members from a number of national societies including, among others, the American Cancer Society, American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), etc.³³ This group reviewed the literature and identified “research gaps” in every area of ovarian cancer research, including risk factors. Talc was not mentioned in any of the research gaps, nor was asbestos. Their review found “heterogeneity in the studies on the use of talcum powder and ovarian cancer risk.”³⁴ The National Comprehensive Cancer Network (NCCN) further states that “Environmental factors have been investigated, such as talc, but so far they have not been conclusively associated with the development of this neoplasm.”³⁵ ACS states in its 2024 Facts and Figures annual publication “The weight of the evidence does not support an association between ovarian cancer and genital exposure to talc-based powder.”³⁶

Similarly, the Ovarian Cancer Research Alliance (OCRA) states that “Research regarding a connection between the use of talcum powder and increased ovarian cancer risk is inconclusive.”³⁷

In March 2024, NCI updated its PDQ on risk factors for ovarian cancer. The NIH-NCI PDQ finds that “[r]esults from case-control studies and cohort studies are inconsistent, so the data are inadequate to support an association between perineal talc exposure and an increased risk of ovarian cancer.”³⁸ The NCI uses a thorough and detailed method to screen for and identify literature pertinent to its committee work.³⁹ Neither the NCI, nor other U.S. National Health Organizations, discussed above, mention nickel, chromium or cobalt exposure as risk factors for ovarian cancer, yet Dr. Judith Wolf (plaintiff’s

³¹ The American College of Obstetricians and Gynecologists. (January 2015, reaffirmed 2019). *Committee Opinion Number 619: Gynecologic Surgery in the Obese Woman*. <https://www.acog.org/-/media/project/acog/acogorg/clinical/files/committee-opinion/articles/2015/01/gynecologic-surgery-in-the-obese-woman.pdf>.

³² Workowski, K. A., & Bolan, G. A. (2015). Sexually transmitted diseases treatment guidelines, 2015. MMWR. Recommendations and reports: *Morbidity and mortality weekly report. Recommendations and reports*, 64(RR-03), 1-137. <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6403a1.htm>.

³³ Burke, W., et al. Executive Summary of the Ovarian Cancer Evidence Review Conference with Appendices, Appendix 1. *Obstet Gynecol*. 2023; 142:179-95.

³⁴ Burke, W., et al. Executive Summary of the Ovarian Cancer Evidence Review Conference with Appendices, Appendix 1. *Obstet Gynecol*. 2023; 142:179-95.

³⁵ National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer. Version 1.2024, MS-3.

³⁶ American Cancer Society. (2024). Cancer Facts & Figures 2024. *American Cancer Society*.

³⁷ Ovarian Cancer Research Alliance: *Risk Factors* (last accessed October 1, 2023) <https://ocrahope.org/patients/about-ovarian-cancer/risk-factors/>.

³⁸ National Cancer Institute, *Ovarian, Fallopian Tube and Primary Peritoneal Cancer Prevention (PDQ): Who is at Risk?* (updated March 6, 2024) https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq#cit/section_1.11.

³⁹ Manrow, R. E., Beckwith, M., & Johnson, L. E. (2014). NCI's Physician Data Query (PDQ®) Cancer Information Summaries: History, Editorial Processes, Influence, and Reach. *Journal of Cancer Education*, 29(1), 198-205.

Gynecologic Oncology expert in this case) has concluded that these metals are carcinogenic to the ovary, referencing IARC.⁴⁰ There is no evidence that these metals are carcinogenic to the ovary.

IARC 2010⁴¹ concluded that there is “Limited evidence in humans for the carcinogenicity of perineal use of talc-based body powder.” (p 412) It should be noted that IARC’s definition of “Limited Evidence of Carcinogenicity” is one that the Working Group considered to be credible, “but chance, bias or confounding could not be ruled out with reasonable confidence.” (p 34) IARC’s overall evaluation stated that “Perineal use of talc-based body powder is *possibly carcinogenic to humans (Group 2B)*.”

IARC 2010 stated that bias could not be ruled out, and we have seen now more than two dozen case-control studies published with the same biases, including selection bias and recall bias. Also, Dr. Linda Cook et al. in 1997 (now 27 years ago), stated near the end of their discussion, “We recommend that cohort studies address this question; these studies could eliminate concerns regarding the potential differences in the reporting of genital powder exposures between cases and controls.”⁴²

The IARC 2010 literature review and references only included data through 2006. Eighteen years have passed since the review of this data, and four well designed prospective cohort studies have been completed and recently pooled by O’Brien et al.,⁴³ including the Nurses’ Health Study, Nurses’ Health Study II, Sister Study, and the Women’s Health Initiative Observational Study. These four prospective cohort studies have included 252,745 women and a total of 3.8 million person-years at risk.⁴⁴ The conclusion is that talcum powder does not cause or contribute to the development of ovarian cancer.

IARC 2012 was the most recent monograph published on Arsenic, Metals, Fibres, and Dusts as a review of human carcinogens.⁴⁵ Within the IARC 2012 monograph is a section on asbestos and ovarian cancer. IARC noted that the published literature examining asbestos exposure and ovarian cancer is “relatively sparse.” Based on 5 studies with heavy occupational exposure to asbestos, the IARC Working Group concluded that there is a probable causal relationship between asbestos and ovarian cancer. These 5 studies were done in women working in gas mask factories and other industries during or around the time of World War II, about 70 years ago. IARC also found support for causation based on studies showing that women with environmental exposure had positive, though not statistically significant, increased incidence of ovarian cancer. However, IARC also noted the possibility of misclassification. This is of particular concern since the published studies relied on death certificates. It has only recently been technologically possible to reliably distinguish pathologically between peritoneal mesothelioma and ovarian cancer. Misclassification would inflate any observed association. Additionally, none of the

⁴⁰Amended Rule 26 Expert Report of Judith Wolf, MD dated November 15, 2023, p.12.

⁴¹ International Agency for Research on Cancer. (2010). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 93. Carbon Black, Titanium Dioxide, and Talc*. Lion, France: IARC, p. 1-413.

⁴² Cook, L. S., Kamb, M. L., & Weiss, N. S. (1997). Perineal powder exposure and the risk of ovarian cancer. *American Journal of Epidemiology*, 145(5), 459-465.

⁴³ O’Brien, K. M., Tworoger, S. S., Harris, H. R., Anderson, G. L., Weinberg, C. R., Trabert, B., ... & Wentzensen, N. (2020). Association of powder use in the genital area with risk of ovarian cancer. *JAMA*, 323(1), 49-59.

⁴⁴ O’Brien, K. M., Tworoger, S. S., Harris, H. R., Anderson, G. L., Weinberg, C. R., Trabert, B., ... & Wentzensen, N. (2020). Association of powder use in the genital area with risk of ovarian cancer. *JAMA*, 323(1), 49-59.

⁴⁵ International Agency for Research on Cancer. (2012). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 100C. Arsenic, Metals, Fibres, and Dusts*. Lion, France: IARC, p. 1-501.

studies reviewed by the IARC Working Group controlled for risk factors that are known to be associated with the development of ovarian cancer.⁴⁶ Slomovitz et al summarized the faults of the IARC 2012 monograph in 2020.⁴⁷ They highlighted the need for expert pathology review. The diagnosis of peritoneal mesothelioma was not added to the ICD-9 (International Classification of Diseases) diagnosis group until 1999, several decades after the studies cited in the IARC 2012 monograph. Also of note, per the Slomovitz review, the IARC 2012 working group reviewed several papers that showed a non-significant risk of ovarian cancer but failed to cite these.⁴⁸

Dalsgaard et al. published two manuscripts in 2022 detailing their research with regard to the incidence of cancer after childhood environmental exposure to asbestos. In both papers, there was actually a reduction in risk of ovarian cancer in children exposed to asbestos with the Standardized Incidence Ratios (SIR) 0.71 (0.5-0.99) and 0.25 (0.15-0.41).^{49 50} Vidican et al. detailed these disease misclassifications in their 2022 paper. In fact, of their 254 enrolled patients, 27 were excluded after expert pathology review due to histologic misclassification. They studied the risk of developing ovarian cancer with asbestos exposure and subdivided their subjects by histologic subtype. They also included family history in their data set. When analysis controlled for family history, there was no association between asbestos exposure and ovarian cancer.⁵¹

Authors from NCI and the National Institute of Environmental Health Sciences published a summary of the epidemiologic evidence regarding the potential association of talc, body powder and ovarian cancer in 2021.⁵² They concluded that “Given the inability to attribute a clear causal factor to the observed associations, the lack of a good experimental model, the lack of a specific biomarker for powder related carcinogenesis, and the inability to rule out confounding by indication, it is difficult to conclude that the observed associations are causal. Furthermore, given the widespread use of powders and the rarity of ovarian cancer, the case for public health relevance is limited. Future work on understanding the association of powder use and ovarian cancer risk should focus both on existing data and new studies. Given that the association from case-control studies may be exaggerated by recall bias and the association from cohort studies may be underestimated because of limited exposure information and

⁴⁶ International Agency for Research on Cancer. (2010). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 93. Carbon Black, Titanium Dioxide, and Talc*. Lyon, France: IARC, p. 1-413.

⁴⁷ Slomovitz, B., De Haydu, C., Taub, M., Coleman, R. L., & Monk, B. J. (2021). Asbestos and ovarian cancer: examining the historical evidence. *International Journal of Gynecologic Cancer*, 31(1), 122-128.

⁴⁸ Slomovitz, B., De Haydu, C., Taub, M., Coleman, R. L., & Monk, B. J. (2021). Asbestos and ovarian cancer: examining the historical evidence. *International Journal of Gynecologic Cancer*, 31(1), 122-128.

⁴⁹ Dalsgaard, SB., et al. Cancer incidence and risk of multiple cancers after environmental asbestos exposure in childhood—A long-term register-based cohort study. *International Journal of Environmental Research and Public Health*. 2022; 19(1):268.

⁵⁰ Dalsgaard SB, et al. A Cohort Study on Cancer Incidence among women Exposed to Environmental Asbestos in Childhood with a Focus on Female Cancers, including Breast Cancer. *Int J Environ Res Public Health*. 2022 Feb 13;19(4):2086.

⁵¹ Vidican P., et al. Frequency of Asbestos Exposure and Histological Subtype of Ovarian Carcinoma. *International Journal of Environmental Research and Public Health*, 2022; 19(9):5383.

⁵² Wentzensen, N., & O'Brien, K. M. (2021). Talc, body powder, and ovarian cancer: A summary of the epidemiologic evidence. *Gynecologic Oncology*, 163(1), 199-208.

attenuation in effects over time since exposure assessment, the association probably lies between these estimates.”⁵³ Importantly, this work was funded by the Intramural Research Program of the NIH.

Also in 2021, IARC and NCI joined in publishing an expert consensus on future research in ovarian cancer titled “Joint IARC/NCI International Cancer Seminar Series Report: expert consensus on future directions for ovarian carcinoma research.”⁵⁴ Both institutions were well represented by co-authors who are experts in the field. Neither talc nor asbestos was mentioned as a research priority in ovarian cancer. In fact, the authors state specifically that “With the exception of oral contraceptive use, the field has not established modifiable risk factors for HGSCs, which are associated with the poorest prognosis.”⁵⁵ This supports my opinion that avoiding talcum powder is not supported as a modifiable risk factor by IARC or the NCI, a division of the NIH.

Health Canada published its final report on talc in April 2021.⁵⁶ I have several concerns about this report. First, the report admits that about half of the case-control studies show no significant difference between cancers and controls. Particularly with regard to meta-analyses, they state: “Collectively, across the three most recent meta-analyses, there were 30 case-control studies and four cohort design studies. A high percentage of the case-control studies, 89% for Berge et al. (2018), 92% for Penninkilampi and Eslick (2018) and 85% for Taher et al. (2019), had calculated ORs greater than 1 (indicating a positive association). Approximately half of these were statistically significant. Three of the four cohort studies also reported ORs greater than 1. However, none were found to be statistically significant (Berge et al. 2018; Penninkilampi and Eslick 2018; Taher et al. 2019).”⁵⁷ Health Canada then goes on to admit the limitations of case-control studies, such as small sample size, limited exposure information collected, reliance on self-reporting, low response rates and potential for recall bias. Health Canada indicates, at Table 7-1, that Penninkilampi and Eslick,⁵⁸ while published in 2018, included the cohort study published by Gertig,⁵⁹ but failed to include the cohort study by Gates⁶⁰ published in 2010. Importantly, Gates 2010 added more than a decade of additional data (with a total of 33 years of follow-up) to the Gertig study and concluded that there is no relationship between talcum powder and ovarian

⁵³ Wentzensen, N., & O'Brien, K. M. (2021). Talc, body powder, and ovarian cancer: A summary of the epidemiologic evidence. *Gynecologic Oncology*, 163(1), 199-208.

⁵⁴ Virani, S., Baiocchi, G., Bowtell, D., Cabaasag, C. J., Cho, K. R., Fortner, R. T., ... & Trabert, B. (2021). Joint IARC/NCI International Cancer Seminar Series Report: expert consensus on future directions for ovarian carcinoma research. *Carcinogenesis*, 42(6), 785-793.

⁵⁵ Virani, S., Baiocchi, G., Bowtell, D., Cabaasag, C. J., Cho, K. R., Fortner, R. T., ... & Trabert, B. (2021). Joint IARC/NCI International Cancer Seminar Series Report: expert consensus on future directions for ovarian carcinoma research. *Carcinogenesis*, 42(6), 785-793.

⁵⁶ Environment and Climate Change/Health Canada. (April 2021). *Screening Assessment Talc (Mg3H2(SiO3)4)*, En84-227/2021E-PDF.

⁵⁷ Environment and Climate Change/Health Canada. (April 2021). *Screening Assessment Talc (Mg3H2(SiO3)4)*, En84-227/2021E-PDF.

⁵⁸ Penninkilampi, R., & Eslick, G. D. (2018). Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. *Epidemiology*, 29(1), 41-49.

⁵⁹ Gertig, D. M., Hunter, D. J., Cramer, D. W., Colditz, G. A., Speizer, F. E., Willett, W. C., & Hankinson, S. E. (2000). Prospective study of talc use and ovarian cancer. *Journal of the National Cancer Institute*, 92(3), 249-252.

⁶⁰ Gates, M. A., Rosner, B. A., Hecht, J. L., & Tworoger, S. S. (2010). Risk factors for epithelial ovarian cancer by histologic subtype. *American Journal of Epidemiology*, 171(1), 45-53.

cancer with regard to the papillary serous cell type.⁶¹ Dr. Wolf also relies on Health Canada, as well as Penninkilampi and Eslick, despite the faults and biases mentioned in this expert report. I have several additional concerns regarding the Health Canada final document, which are detailed below.

Bradford Hill Criteria, Health Canada

Health Canada briefly reviews all of the Bradford Hill considerations and then goes on to state that it will primarily rely on the following four:

- Strength of Association
- Consistency
- Biologic Gradient (Dose response)
- Biologic Plausibility⁶²

Health Canada acknowledges that there is no biologic gradient demonstrated in the relevant studies.⁶³ When discussing biologic plausibility, the authors state that “a specific order of events by which perineal talc exposure could lead to ovarian cancer has not been established.”⁶⁴ After this statement, the authors state that several recent publications support biologic plausibility (Campion et al. 2018; Fletcher et al. 2019; McDonald et al. 2019; McDonald et al. 2019; Mandarino et al. 2020).⁶⁵ However, Health Canada fails to mention that each one of these five publications is authored or co-authored by a paid plaintiffs’ expert in talc litigation. The authors state that case-control studies are consistent, yet they previously stated (as noted above) that about half of the case-control studies were not statistically significant.⁶⁶ Additionally, Health Canada states that talc burden could possibly be due to sample contamination.⁶⁷ It mentions recall bias but dismisses it.⁶⁸ Based on these factors, I do not agree with the conclusions of Health Canada. There are likely dozens, if not hundreds, of other governmental health agencies across the globe that issue various opinions based on their review of health-related issues. I have never relied on Health Canada or any other country’s health agency’s recommendations in the past. I rely on U.S. governmental agencies for advice with regard to health risks, such as the FDA, CDC, NIH, NCI, NCCN and national organizations such as SGO and ACOG.

⁶¹ Gates, M. A., Rosner, B. A., Hecht, J. L., & Tworoger, S. S. (2010). Risk factors for epithelial ovarian cancer by histologic subtype. *American Journal of Epidemiology*, 171(1), 45-53.

⁶² *Environment and Climate Change/Health Canada. (April 2021). Screening Assessment Talc (Mg3H2(SiO3)4), En84-227/2021E-PDF*, p. 29.

⁶³ *Environment and Climate Change/Health Canada. (April 2021). Screening Assessment Talc (Mg3H2(SiO3)4), En84-227/2021E-PDF*, p. 33.

⁶⁴ *Environment and Climate Change/Health Canada. (April 2021). Screening Assessment Talc (Mg3H2(SiO3)4), En84-227/2021E-PDF*, p. 33.

⁶⁵ *Environment and Climate Change/Health Canada. (April 2021). Screening Assessment Talc (Mg3H2(SiO3)4), En84-227/2021E-PDF*, p. 33.

⁶⁶ *Environment and Climate Change/Health Canada. (April 2021). Screening Assessment Talc (Mg3H2(SiO3)4), En84-227/2021E-PDF*, p. 30-33.

⁶⁷ *Environment and Climate Change/Health Canada. (April 2021). Screening Assessment Talc (Mg3H2(SiO3)4), En84-227/2021E-PDF*, p. 34.

⁶⁸ *Environment and Climate Change/Health Canada. (April 2021). Screening Assessment Talc (Mg3H2(SiO3)4), En84-227/2021E-PDF*, p. 35.

FDA

On April 1, 2014, the FDA issued a letter to Dr. Samuel S. Epstein⁶⁹ denying a Citizens' Petition. The denial states that the "FDA did not find that the data submitted presented conclusive evidence of a causal association between talc use in the perineal area and ovarian cancer."⁷⁰ The FDA stated on page 5 of its letter: "While there exists no direct proof of talc and ovarian carcinogenesis, the potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable."⁷¹ There were no citations provided to support this statement, and in my opinion, this statement is not supported based on the barriers of the female reproductive tract, or by the literature related to the theory of migration. My opinions related to the theory of migration are detailed later in this report and are based on over 30 years of clinical experience in the fields of Obstetrics and Gynecology as well as the sub-specialty of Gynecologic Oncology.

EPIDEMIOLOGY – GENERAL CONCEPTS

Types of Epidemiologic studies

Prospective Randomized Studies

For any scientific question, the prospective randomized study is the gold standard and eliminates most forms of bias. Prospective randomized studies assign half the participants with the exposure of interest prior to the development of the outcome of interest. In many cases, these are very expensive, and they can also be impractical, impossible, or unethical to implement. For purposes of the study of talcum powder use and its relationship to ovarian cancer, we are limited to case-control studies, meta-analyses, and prospective cohort studies. There is a hierarchy of relevance, which is well accepted in the medical and scientific community, with case reports being the lowest quality and least reliable, then case-control studies, then prospective cohorts, then prospective randomized studies as the highest quality and most reliable.

Case Reports

Case reports, the simplest, easiest and most basic form of scientific publication, simply report a unique observation in a particular case or small group of cases. They are also the most biased in that there are no comparison groups. When a series of case reports note similar observations, they are generally followed up with case-control studies.

⁶⁹ Food and Drug Administration Letter from Musser SM to Epstein SS Re: Docket Numbers 94P-0420 and FDA-2008-P-0309-0001/CP. Date stamped: April 1, 2014. April 1, 2014 FDA Denial of 1994 and 2008 Petitions.

⁷⁰ Food and Drug Administration Letter from Musser SM to Epstein SS Re: Docket Numbers 94P-0420 and FDA-2008-P-0309-0001/CP. Date stamped: April 1, 2014. April 1, 2014 FDA Denial of 1994 and 2008 Petitions, p. 1.

⁷¹ Food and Drug Administration Letter from Musser SM to Epstein SS Re: Docket Numbers 94P-0420 and FDA-2008-P-0309-0001/CP. Date stamped: April 1, 2014. April 1, 2014 FDA Denial of 1994 and 2008 Petitions, p. 1.

Case-Control Studies

Case-control studies are, by design, biased. In case-control studies, subjects are identified based on the presence or absence of disease and then asked about their past exposures. Controls are frequently obtained by either random phone calls, electoral rolls, hospitalized patients or other methods that can introduce selection bias. Case-control studies can offer value in that they are a relatively simple and inexpensive method of working through a hypothesis. Of the case-control studies that have looked at the relationship between talcum powder use and ovarian cancer, roughly half show no association between genital talc use and ovarian cancer, and the other half show a weak association (see table below). All have similar inherent biases, including, but not limited to: selection bias, recall bias, and some have observer/author bias. When case-control studies show a trend or a suspected association, they are generally followed up with cohort studies to confirm or refute the potential association.

Cohort Studies

Prospective cohort studies are far less prone to bias. In prospective cohort studies, subjects are identified as exposed or not exposed prior to developing disease and followed prospectively. Selection bias is avoided due to the fact that tens of thousands of persons are enrolled (i.e., Nurses' Health Study, Sister Study, Women's Health Initiative) without regard to who will or will not ultimately develop a disease. They are also enrolled without regard to who is or is not exposed to a particular element. They are then followed over time and queried as to various health outcomes and potential risk factors of interest. Loss to follow-up can be a potential source of bias in prospective cohort studies in that select patients may drop out of the study for various reasons; therefore, the final statistical analysis should take this into account. In the case of talc and ovarian cancer, we have four prospective cohort studies, which have been pooled together by O'Brien et al., which includes more than 250,000 women and 3.8 million person-years of follow up.⁷²

TALC EPIDEMIOLOGY**Case-Control Studies**

There are 24 case-control studies published on the proposed association of talc and ovarian cancer (excluding the four case-control studies in the literature reporting on duplicative data sets). Of these 24 case-control studies, 13 showed a statistically significant association. The other 11 case-control studies showed no statistically significant association.

Below is a table listing the case-control studies that do not show a statistically significant association between talcum powder use and ovarian cancer, as well as those that do show an association:

⁷² O'Brien, K. M., Tworoger, S. S., Harris, H. R., Anderson, G. L., Weinberg, C. R., Trabert, B., ... & Wentzensen, N. (2020). Association of powder use in the genital area with risk of ovarian cancer. *JAMA*, 323(1), 49-59.

Case Control Study Summary Table						
Case Control Studies with no Significant Difference between Cancers and Controls						
	Author	Year	O.R./R.R.	C.I.	Application	Cases Controls
1	Hartge	1983	0.70	0.40-1.10	Any talc use	197 197
2	Whittemore	1988	1.30	0.88-1.92	Overall trend, 30/mo, perineum	188 539
3	Booth	1989	1.30	0.8-1.9	Daily Genital talc use	235 451
4	Harlow	1992	1.50	1.00-2.1	Any genital talc use	235 239
5	Rosenblatt	1992	1.00	0.20-4.00	Any genital talc use	77 46
6	Chen	1992	3.90	0.9-10.63	Lower abdomen and perineum	112 224
7	Tzonou	1993	1.05	0.28-3.98	Perineal talc use	189 200
8	Godard	1998	2.49	0.94-6.58	Perineal talc use, ever vs never	170 170
9	Wong	1999	1.00	0.80-1.3	Genital or thigh use	499 755
10	Moorman	2009	1.19	0.68-2.09	Any Talc Use African American	143 189
10	Moorman	2009	1.04	0.82-1.33	Any Talc Use White	943 868
11	Rosenblatt	2011	1.27	0.97-1.66	Perineal use after bathing	812 1313
Case Control Studies with Significant Difference between Cancers and Controls						
	Author	Year	O.R.	C.I.	Application	Cases Controls
1	Cramer	1982	1.92	1.27-2.89	Any perineal exposure	215 215
2	Green	1997	1.30	1.1-1.6	Ever used talc in perineal region	824 855
3	Chang	1997	1.42	1.08-1.86	Any talc exposure (napkins/perineum)	450 564
4	Cook	1997	1.50	1.1-2.0	Lifetime genital application- any	329 521
5	Ness	2000	1.50	1.1-2.0	Genital/Rectal talc use	767 1367
6	Mills	2004	1.37	1.02-1.85	Ever used talc in perineal region	256 1122
7	Merrit	2008	1.17	1.01-1.36	Ever used talc in perineal region	1576 1509
8	Gates	2008	1.41	1.10-1.79	Daily genital talc use (NECC only)	1175 1202
9	Kurta	2012	1.40	1.16-1.69	Perineal talc use	902 1802
10	Wu	2015	1.46	1.27-1.69	All races, any genital talc use	1701 2391
11	Shildkraut	2016	1.44	1.11-1.86	Any genital talc use	584 745
12	Cramer	2016	1.33	1.16-1.52	Genital talc use	2041 2100
13	Davis	2021	1.32	1.17-1.48	Genital powder use	3420 7881
Studies with duplicative patient populations						
	Purdie	1995	1.27	1.04-1.54	Talc around abdomen/perineum	824 860
	Cramer	1999	1.60	1.18-2.15	Any personal genital exposure	563 523
	Pike	2004	1.60	1.18-2.18	Genital talc use (yes vs no)	477 660
	Wu	2009	1.53	1.13-2.09	Talc use perineal area (yes vs no)	609 688

Case-control studies that do not show a statistically significant association

There are 11 case-control studies that found no association between talc use and ovarian cancer. These publications make up nearly half of all published case-control studies and demonstrate the lack of consistency in the epidemiologic data.

Hartge et al., 1983⁷³ studied 197 ovarian cancer cases and compared them to 197 controls in the Washington, D.C. area. Their study was published as a letter to the editor in response to the Cramer et al. publication in 1982. The authors found no overall association between talc use and ovarian cancer. They also pointed out that talc use on diaphragms, which places the talcum powder anatomically closer

⁷³ Hartge, P., Hoover, R., Leshner, L. P., & McGowan, L. (1983). Letter to the Editor: Talc and ovarian cancer. *JAMA*, 250(14), 1844.

to the ovaries than genital powder use, showed no associated risk. Hartge also pointed out potential bias in Cramer's case-control study, including: chance, bias in selection, bias in observation, confounding variables as well as the differences in cases vs controls in their recollection of talcum powder use. Other potential bias included the fact that controls were interviewed in the hospital while cases were interviewed at home. The authors also pointed out the possibility that talc itself does not increase the risk of ovarian cancer, but that patients with ovarian cancer may have or perceive a greater need for using body powder in the genital area for reasons related either to the biology of the disease or to lifestyle.

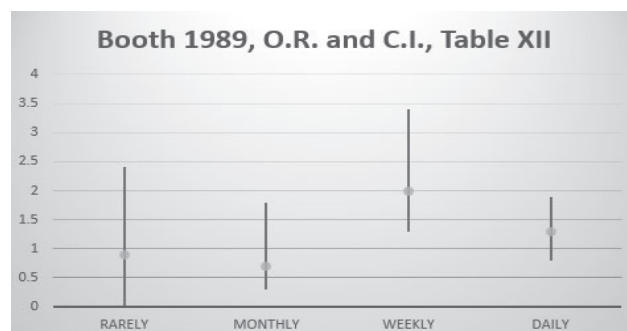
Whittemore et al., 1988⁷⁴ studied 188 cases and compared them to 539 controls. While they did not find an association between talc use and ovarian cancer (R.R. 1.30, C.I. 0.88-1.92), they did note an association between coffee consumption and ovarian cancer (R.R. 3.41, C.I. 1.46-7.96). Importantly, with regard to talc use, there was no dose-response noted (no association found for 1-20 applications per month (R.R. 1.27, C.I. 0.82-1.96), 20+ applications per month (R.R. 1.45, C.I. 0.94-2.22), or 30 applications per month (R.R. 1.30, C.I. 0.88-1.92)).

Booth et al. 1989⁷⁵ studied 235 cases compared to 451 controls in London and Oxford, England. The only association of ovarian cancer with talc use was seen with weekly use (R.R. 2.0, C.I. 1.3-3.4). Those patients who used talc rarely, monthly or even daily were not found to be at increased risk. The bar graph below demonstrates no clear trend of dose-response.

Table XII Relative risks for ovarian cancer associated with reported frequency of talc use in the genital area

	Cases	Controls	RR	(95% CI)
Reported frequency of talc use ^b				
Never	76	178	1.0*	
Rarely	6	16	0.9	(0.3-2.4)
Monthly	7	24	0.7	(0.3-1.8)
Weekly	57	77	2.0	(1.3-3.4)
Daily	71	139	1.3	(0.8-1.9)
χ^2 for trend = 3.80, $P = 0.05$				

Relative risks adjusted for age and social class. *Reference category.
^bData missing for 18 (8%) cases and 17 (4%) controls as questions on talc use introduced three months after study began.



Harlow et al. 1992⁷⁶ reported on 235 ovarian cancer cases compared to 239 controls in 10 Boston hospitals. They found no association with any genital talc use (O.R. 1.5, C.I. 1.0-2.1). Below is Table 3

⁷⁴ Whittemore, A. S., Wu, M. L., Paffenbarger Jr, R. S., Sarles, D. L., Kampert, J. B., Grosser, S., ... & Hendrickson, M. (1988). Personal and environmental characteristics related to epithelial ovarian cancer: II. Exposures to talcum powder, tobacco, alcohol, and coffee. *American Journal of Epidemiology*, 128(6), 1228-1240.

⁷⁵ Booth, M., Beral, V., & Smith, P. (1989). Risk factors for ovarian cancer: a case-control study. *British Journal of Cancer*, 60(4), 592-598.

⁷⁶ Harlow, B. L., Cramer, D. W., Bell, D. A., & Welch, W. R. (1992). Perineal exposure to talc and ovarian cancer risk. *Obstetrics and Gynecology*, 80(1), 19-26.

from Harlow et al., which demonstrates a lack of dose-response. Of the 9 rows of data, 8/9 show no significant difference, and the only significant O.R. is the last line in the table.

Applications	Cases	Controls	Adjusted OR*	95% CI
Total applications				
None	121	145	1.0	
<1000	18	19	1.3	→ 0.7-2.7
1000-10,000	54	44	1.5	→ 0.9-2.4
>10,000	42	31	1.8	→ 1.0-3.0
χ^2 1df test for linear trend = 2.85, $P = .094^*$				
Applications excluding use after hysterectomy or tubal ligation				
None	121	145	1.0	
<1000	19	19	1.4	→ 0.7-2.9
1000-10,000	57	46	1.5	→ 0.9-2.4
>10,000	38	29	1.7	→ 1.0-3.0
χ^2 1df test for linear trend = 3.19, $P = .077^*$				
Applications excluding use after hysterectomy or tubal ligation, and use during nonovulatory months [†]				
None	124	149	1.0	
<1000	24	23	1.5	→ 0.8-2.9
1000-10,000	55	51	1.3	→ 0.8-2.0
>10,000	32	16	2.8	→ 1.4-5.4
χ^2 1df test for linear trend = 6.15, $P = .015^*$				
Abbreviations as in Table 2.				
* Adjusted for parity (0, 1-2, >2), education (<12 years, >12 years), marital status (never married, ever married), religion (Jewish, non-Jewish), use of sanitary napkins (no, yes), douching (no, yes), age (continuous), and weight (<140 lb, ≥140 lb).				
† Trend test based on actual applications as a continuous variable.				
‡ Excludes exposures while taking oral contraceptives, while pregnant or breast-feeding, or occurring after menopause. There were three cases and four controls who moved from "exposed" to "nonexposed" in this category, as all of the exposure occurred during oral contraceptive use, pregnancies, or after menopause.				

Rosenblatt et al., 1992⁷⁷ studied 77 cases and compared them to 46 controls. As demonstrated in Table 3 below, of the 10 rows of data, only one (sanitary napkin with talc exposure) showed statistical significance. "Diaphragm use with powder," which places the powder as anatomically close to the ovary as possible, was not associated with ovarian cancer. Nor was condom use, which also should thrust the powder into the cervical os during coitus, placing the powder closer to the ovaries. "Genital fiber" use, yes vs no was not associated with cancer, nor was length of use of genital fiber (≥ 37.4 years vs < 37.4 years).

⁷⁷ Rosenblatt, K. A., Szklo, M., & Rosenshein, N. B. (1992). Mineral fiber exposure and the development of ovarian cancer. *Gynecologic Oncology*, 45(1), 20-25.

TABLE 3
Number and Frequency Distribution of Cases and Controls with Odds Ratios for Genital Fiber Exposure
and Other Related Variables

Exposure interval	Attribute	Cases		Controls		Odds ratio	95% confidence interval
		N	%	N	%		
Genital fiber use	Yes	67	87.0	40	88.0	1.0	0.2–4.0 ^b
	No	10	13.0	5	11.1		
	Missing	0		1			
Length of use of genital fiber ^a (years)	≥37.4	39	55.7	16	39.0	2.4	1.0–5.8 ^c
	<37.4	31	44.3	25	61.0		
	Missing	7		5			
(Median of cases and controls)	Median		41.9		24.0		
Ovarian biopsies	Yes	6	7.8	3	6.5	1.1	0.3–4.4
	No	71	92.2	43	93.5		
Unilateral oophorectomy	Yes	8	10.4	5	10.9	0.8	0.2–2.5 ^d
	No	69	89.6	41	89.1		
Tubal ligation	Yes	4	5.2	6	13.0	0.2	0.3–0.9 ^{d,e}
	No	73	94.8	40	87.0		
Hysterectomy	Yes	19	24.7	12	26.1	0.7	0.3–1.7 ^d
	No	58	75.3	34	73.9		
Condom use	Yes	35	49.3	22	51.2	1.6	0.6–3.9 ^{b,d}
	No	37	50.7	21	48.8		
	Missing	5		3			
Diaphragm use with powder	Yes	14	18.9	5	11.4	3.0	0.8–10.8 ^{b,d}
	No	60	81.1	39	88.6		
	Missing	3		2			
Genital bath talc	Yes	22	28.9	8	18.6	1.7	0.7–3.9
	No	54	71.0	35	81.4		
	Missing	1		3			
Sanitary napkin with talc exposure	Yes	21	30.0	6	13.6	4.8	1.3–17.8 ^f
	No	49	70.0	38	86.4		
	Missing	7		2			

^a After subtraction of the time since tubal ligation, for those who had ligation.

^b Adjusted for number of live births.

^c Adjusted for religion.

^d Adjusted for years of education on subject.

^e Adjusted for highest weight 20 years prior to diagnosis.

^f Adjusted for highest weight 1 year prior to diagnosis.

Chen et al., 1992⁷⁸ studied 112 cases compared to 224 controls in Beijing, China. They found an R.R. 3.90, C.I. 0.9-10.63. Despite the fact that this confidence interval crosses one and is not statistically significant, the authors concluded that talc was associated with ovarian cancer. The authors note in their comments several “methodological limitations” which may have impacted the results of the study, including the nature of cancer registration in China, high rate of loss due to deaths, and exclusion of controls with current health problems, all leading to selection bias.

Tzonou et al., 1993⁷⁹ studied 189 cases and compared them to 200 controls in Greater Athens, Greece. They found no statistically significant association between perineal talc use and ovarian cancer (R.R. 1.05, C.I. 0.28-3.98). They did, however, note a dose-dependent relationship to using hair dye and the risk of developing ovarian cancer, particularly with hair dying > 5 times per year (R.R. 2.16, C.I. 1.19-3.89).

⁷⁸ Chen, Y., Wu, P. C., Lang, J. H., GE, W. J., Hartge, P., & Brinton, L. A. (1992). Risk factors for epithelial ovarian cancer in Beijing, China. *International Journal of Epidemiology*, 21(1), 23-29.

⁷⁹ Tzonou, A., Polychronopoulou, A., Hsieh, C. C., Trichopoulos, D., Rebelakos, A., & Karakatsani, A. (1993). Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *International Journal of Cancer*, 55(3), 408-410.

Godard et al., 1998⁸⁰ reported 170 cases compared to 170 controls from Montreal, Canada. They found no association with perineal talc use and ovarian cancer (R.R. 2.49, C.I. 0.94-6.58). This lack of association held true when comparing all case patients, sporadic case patients, and familial case patients.

Wong et al., 1999⁸¹ reported 499 cases vs 755 controls from Roswell Park Cancer Institute. Genital or thigh use of talc was not associated with the development of ovarian cancer (O.R. 1.0, C.I. 0.8-1.3). They also pointed out that talc use, whether by sanitary napkin, genital/thigh use or both showed no association (see Table 2 below).

Table 2. Talc Use by Site: Odds Ratios and 95% Confidence Intervals

Site	Controls	Cases	OR* (95% CI)
Never used	382 (55.1%)	241 (52.2%)	1.0
Sanitary napkin	20 (2.9%)	13 (2.8%)	0.9 (0.4, 2.0)
Genital or thigh area	223 (32.2%)	157 (34.0%)	1.0 (0.8, 1.3)
Both	68 (9.8%)	51 (11.0%)	1.1 (0.7, 1.7)

OR = odds ratio; CI = confidence interval.

* Adjusted for parity, oral contraceptive use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location, and history of tubal ligation or hysterectomy.

Moorman et al., 2009⁸² published a paper studying ovarian cancer risk factors in African-American women and White women. Since the authors broke down their analysis into these two groups defined by race, I have done the same in my table of case-control studies demonstrated previously in this expert report. In African-American women, they studied 143 cases vs 189 controls and found no association between talcum powder use and ovarian cancer (O.R. 1.19, C.I. 0.68-2.09). Similarly, they reported on White women, comparing 943 cases vs 868 controls, and also found no association between talcum powder use and ovarian cancer (O.R. 1.04, C.I. 0.82-1.33).

Rosenblatt et al., 2011⁸³ studied 812 cases compared to 1313 controls in Western Washington State. There was no association when looking at perineal use of talc after bathing (O.R. 1.27, C.I. 0.97-1.66). They noted "no clear pattern of risk increase on the basis of the extent of use, assessed as years in which powder was used, or as lifetime number of applications for invasive or borderline tumors, or their histologic subtypes. There was no alteration in the risk of ovarian cancer associated with other types of powder exposure (e.g., on sanitary napkins or diaphragms)."

⁸⁰ Godard, B., Foulkes, W. D., Provencher, D., Brunet, J. S., Tonin, P. N., Mes-Masson, A. M., ... & Ghadirian, P. (1998). Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. *American Journal of Obstetrics and Gynecology*, 179(2), 403-410.

⁸¹ Wong, C., Hempling, R. E., Piver, M. S., Natarajan, N., & Mettlin, C. J. (1999). Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. *Obstetrics & Gynecology*, 93(3), 372-376.

⁸² Moorman, P. G., Palmieri, R. T., Akushevich, L., Berchuck, A., & Schildkraut, J. M. (2009). Ovarian cancer risk factors in African-American and white women. *American Journal of Epidemiology*, 170(5), 598-606.

⁸³ Rosenblatt, K. A., Weiss, N. S., Cushing-Haugen, K. L., Wicklund, K. G., & Rossing, M. A. (2011). Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes & Control*, 22(5), 737-742.

As demonstrated in Table 2 below, when reviewing the rows of data associated with “Invasive tumors,” only 4/28 (14%) rows show any statistically significant association while 24/28 (86%) demonstrate no association between talcum powder use and ovarian cancer, which supports the authors’ conclusions that their study “yielded results opposite to those that had been observed or hypothesized by others.”⁸⁴ They did find a statistically significant association with borderline tumors; however, these tumors are benign and should not be lumped in with ovarian cancers. Over the last 20 years, criteria for characterizing this subset of tumors has changed, further complicating interpretations of ovarian cancer risk in older studies. Only four rows of data in the “Borderline tumors” column demonstrate any association.

⁸⁴ Rosenblatt, K. A., Weiss, N. S., Cushing-Haugen, K. L., Wicklund, K. G., & Rossing, M. A. (2011). Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes & Control*, 22(5), 742.

Table 2 Risk of epithelial ovarian cancer in relation to the use of perineal powder after bathing by duration and timing of use, overall and among women with borderline and invasive tumors

	Controls (n = 1,313) ^a	Borderline tumors (n = 217) ^a	OR ^b	95% CI	Invasive tumors (n = 595) ^a	OR ^b	95% CI	All tumors (n = 812) ^a	OR ^b	95% CI
Never used ^c	1,161	184	1.00	Ref.	515	1.0	Ref.	699	1.0	Ref.
Duration of use (years)										
1–9.9	38	9	1.33	0.61–2.87	24	1.42	0.83–2.43	33	1.39	0.85–2.28
10–19.9	35	10	1.97	0.93–4.17	19	1.28	0.71–2.29	29	1.46	0.87–2.45
20–34.9	40	10	1.83	0.88–3.80	20	1.11	0.63–1.95	30	1.28	0.78–2.10
35+	38	4	1.08	0.37–3.15	15	0.86	0.46–1.60	19	0.91	0.51–1.62
Lifetime number of applications										
1–1,599	36	6	1.05	0.42–2.61	20	1.26	0.71–2.25	26	1.21	0.71–2.06
1,600–4,799	37	17	3.11	1.67–5.78	28	1.72	1.03–2.88	45	2.08	1.32–3.27
4,800–9,999	39	6	1.19	0.49–2.92	14	0.78	0.41–1.48	20	0.87	0.50–1.53
10,000+	37	4	0.98	0.34–2.85	14	0.84	0.44–1.59	18	0.87	0.48–1.57
Age at first use (years) ^c										
<15	27	4	0.89	0.30–2.66	8	0.67	0.30–1.53	12	0.74	0.37–1.50
15–<20	36	8	1.46	0.64–3.31	19	1.10	0.61–1.97	27	1.20	0.71–2.03
20–<30	43	12	1.93	0.98–3.80	20	1.04	0.59–1.81	32	1.25	0.77–2.03
30+	45	9	1.68	0.79–3.60	32	1.68	1.04–2.72	41	1.69	1.08–2.64
Age at last use (years) ^c										
<35	33	10	1.54	0.72–3.28	15	0.97	0.51–1.83	25	1.14	0.66–1.97
35–<50	39	15	2.07	1.09–3.93	20	1.15	0.65–2.03	35	1.42	0.88–2.31
50–<60	36	6	1.39	0.56–3.44	19	1.20	0.67–2.15	25	1.25	0.73–2.13
60+	43	2	0.64	0.15–2.74	24	1.30	0.76–2.25	26	1.21	0.72–2.05
Calendar year of first use ^c										
≤1959	39	5	1.47	0.55–3.92	14	0.73	0.38–1.40	19	0.86	0.48–1.53
1960–1969	38	4	0.82	0.28–2.38	20	1.18	0.66–2.09	24	1.10	0.65–1.89
1970–1979	38	11	1.65	0.81–3.37	15	0.91	0.49–1.69	26	1.12	0.66–1.89
1980+	36	33	2.20	1.11–4.34	30	1.97	1.18–3.28	43	2.03	1.28–3.24
Time since first use (years) ^c										
≤25	41	12	1.78	0.89–3.54	30	1.76	1.07–2.89	42	1.77	1.12–2.78
25–<38	41	14	1.98	1.03–3.79	24	1.25	0.73–2.13	38	1.46	0.91–2.32
38–<45	34	3	0.79	0.23–2.69	13	0.88	0.45–1.72	16	0.87	0.47–1.61
45+	35	4	1.30	0.44–3.83	12	0.72	0.36–1.43	16	0.82	0.44–1.52
Time since last use (years) ^c										
Current user	70	12	1.35	0.71–2.59	40	1.28	0.85–1.94	52	1.30	0.89–1.91
≤12	26	9	2.11	0.94–4.77	17	1.59	0.83–3.02	26	1.74	0.98–3.10
13–23	27	7	1.80	0.75–4.34	7	0.55	0.24–1.29	14	0.85	0.44–1.66
24+	28	5	1.22	0.45–3.29	14	1.10	0.56–2.17	19	1.13	0.61–2.08

^a Numbers in column may not sum to total due to missing values^b Adjusted for age, calendar year of diagnosis/reference date, county of residence, number of full-term births, and duration of hormonal contraception^c Use defined as regular use after bathing for at least 1 year

In summary, there are 13 publications of various case-control studies with the findings of statistically significant results. All of these 13 studies have similar biases with regard to both selection bias as well as recall bias. Of the 24 case-control studies on this topic published to date, 11/24 (45.8%), show no significant difference in ovarian cancer risk when comparing cancer cases to controls.

Case-control studies that show a statistically significant association

In summary, only 13 of the 24 published case-control studies showed a statistically significant association between talcum powder use and the development of ovarian cancer.

Cramer et al. 1982⁸⁵ studied 215 white females who spoke English with ovarian cancer and 215 controls who were randomly selected from the “Massachusetts Town Books” and were matched by precinct of residence, race and age. Controls were not excluded because of prior hysterectomy or other types of pelvic operations. Per the authors, “Women who had had pelvic operations were generally confident in their knowledge of whether their ovaries had been removed, but the nature of the operations could not be verified by hospital records.”⁸⁶ In my experience of more than 30 years as a pelvic surgeon, about half of women with a history of prior pelvic surgery on whom I have operated are incorrect in their description of what organs were removed; i.e., some women who think their ovaries were removed actually still have one or two remaining tubes and ovaries, some women who think they still have one or two ovaries actually do not. An additional factor introducing bias into the Cramer study is the exclusion of 20 women (4%) because they were the “wrong age or race,” i.e., not white, or did not speak English and the high rate of refusal to participate among potential controls.⁸⁷ The authors state in their discussion: “There is reason for concern that the high refusal rate among the controls may have introduced a selection bias among the controls.”⁸⁸ This statement is prophetic regarding many of the case-control studies published to date. Selection bias and recall bias are prevalent in many case-control studies, likely explaining why 11 case-control studies to date show no significant difference and only 12 show a small significant difference. The meta-analyses amplify this effect.

Green et al. 1997⁸⁹ studied 824 women with ovarian cancer (cases) and compared them to 855 controls who were identified and matched for age and district of residence from the electoral roll in three Australian states. This study found a statistically significant decrease in ovarian cancer in women with prior hysterectomy or tubal ligation. The authors found an increase in ovarian cancer in talc users, though there was “no additional effect of longer duration of talc use.”⁹⁰ However, this study is also affected by recall bias and selection bias.

⁸⁵ Cramer, D. W., Welch, W. R., Scully, R. E., & Wojciechowski, C. A. (1982). Ovarian cancer and talc. A case-control study. *Cancer*, 50(2), 372-376.

⁸⁶ Cramer, D. W., Welch, W. R., Scully, R. E., & Wojciechowski, C. A. (1982). Ovarian cancer and talc. A case-control study. *Cancer*, 50(2), 372-376, p. 373.

⁸⁷ Cramer, D. W., Welch, W. R., Scully, R. E., & Wojciechowski, C. A. (1982). Ovarian cancer and talc. A case-control study. *Cancer*, 50(2), 372-376, p. 373.

⁸⁸ Cramer, D. W., Welch, W. R., Scully, R. E., & Wojciechowski, C. A. (1982). Ovarian cancer and talc. A case-control study. *Cancer*, 50(2), 372-376, p. 375.

⁸⁹ Green, A., Purdie, D., Bain, C., Siskind, V., Russell, P., Quinn, M., & Ward, B. (1997). Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. *International Journal of Cancer*, 71(6), 948-951.

⁹⁰ Green, A., Purdie, D., Bain, C., Siskind, V., Russell, P., Quinn, M., & Ward, B. (1997). Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. *International Journal of Cancer*, 71(6), 949.

Chang et al. 1997⁹¹ studied 450 patients and compared them to a control group of 564 women recruited from 873 who were identified as eligible. 30.2% refused to participate as a control, 1.9% were too ill and 3.2% were lost to follow-up. There was a significant difference in cases vs controls. Women with cancer were more likely to have a mother or a sister with ovarian or breast cancer, women without cancer (controls) had a greater number of full-term pregnancies and a higher percentage of BTL or hysterectomy. In Table 2 (p 2399), of the 15 rows of data reporting results on talc exposure (i.e., excluding those results related to cornstarch exposure), 12 of the 15 rows show no statistically significant difference, with the confidence intervals crossing one. There is no dose-response relationship. For example, women with < 30 years of after-bath talc use had an O.R. 1.697 (C.I. 1.09-2.64) which might lead one to conclude that there is a relationship. However, for a woman with 30-40 years use and > 40 years of after-bath talc use, the results showed no statistically significant difference. Despite this, the authors note “A questionable dose-response relationship was observed between duration or frequency of exposure and risk.”⁹² This statement is simply not supported by their data.

Cook et al. 1997⁹³ studied 313 cases vs 422 controls. Results in Table 3 (p 463) show findings similar to Chang et al. Of the 20 rows of data, 17/20 (85%) show no statistically significant difference. In table 4 (p 464), which looks at various factors and makeups of the powders, none of the results reach statistical significance. Despite the lack of statistically significant findings, the authors conclude that a “history of perineal dusting or use of genital deodorant sprays has a modest influence on the development of epithelial ovarian tumors.” The vast majority of the results in Tables 3 and 4 showed no significant difference between cases and controls (i.e., the two groups were reported as similar):

⁹¹Chang, S., & Risch, H. A. (1997). Perineal talc exposure and risk of ovarian carcinoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, 79(12), 2396-2401.

⁹² Chang, S., & Risch, H. A. (1997). Perineal talc exposure and risk of ovarian carcinoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, 79(12), 2400.

⁹³ Cook, L. S., Kamb, M. L., & Weiss, N. S. (1997). Perineal powder exposure and the risk of ovarian cancer. *American Journal of Epidemiology*, 145(5), 459-465.

TABLE 3. Relative risk of epithelial ovarian cancer associated with genital powder use by methods of powder application: King, Pierce, and Snohomish counties, Washington State, 1986–1988*

Lifetime genital powder application	Ovarian cancer cases (n = 313)		Controls (n = 422)		RR†	95% CI‡
	No	%	No	%		
None	154	49.2	256	60.7	1.0	Referent
Any perineal dusting	95	30.4	87	20.6	1.6	1.1–2.3
Cumulative lifetime days						
≤2,000	20	6.4	22	5.2	1.8	0.9–3.5
2,001–5,000	24	7.7	26	6.2	1.5	0.9–2.9
5,001–10,000	21	6.7	22	5.2	1.2	0.6–2.4
>10,000	28	8.9	17	4.0	1.8	0.9–3.4
Unknown	2	0.6	0			
Diaphragm storage in powder	46	14.7	51	12.1	1.0	0.6–1.6
Cumulative lifetime months						
≤60	24	7.7	26	6.2	1.1	0.6–1.9
>60	15	4.8	20	4.7	0.8	0.4–1.7
Unknown	7	2.2	5	1.2		
Usually washed before use						
No	19	6.1	14	3.3	1.4	0.7–3.0
Yes	20	6.4	31	7.3	0.7	0.4–1.4
Unknown	7	2.2	6	1.4		
Any powder on sanitary napkins	38	12.1	40	9.5	0.9	0.5–1.5
Cumulative lifetime months						
≤120	25	8.0	21	5.0	1.3	0.7–2.4
>120	12	3.8	19	4.5	0.5	0.2–1.1
Unknown	1	0.3	0			
Lifetime applications						
≤1,000	23	7.3	19	4.5	1.3	0.7–2.5
>1,000	14	4.5	21	5.0	0.6	0.3–1.2
Unknown	1	0.3	0			
Any genital deodorant spray	40	12.8	40	9.5	1.9	1.1–3.1
Cumulative lifetime months						
≤12	24	7.7	31	7.4	1.5	0.9–2.8
>12	15	4.8	9	2.1	2.7‡	1.1–6.6
Unknown	1	0.3	0			
Lifetime applications						
≤500	29	9.3	34	8.1	1.7	1.0–2.9
>500	10	3.2	6	1.4	2.6‡	0.9–7.6
Unknown	1	0.3	0			

* Numbers do not add up to total cases and controls because women may have used a variety of methods for powder application.

† RR, relative risk, adjusted for age and for the other methods of genital powder application (none, any), CI, confidence interval.

‡ p value for trend < 0.05.

TABLE 4. Relative risk of epithelial ovarian cancer associated with type of powder used with perineal dusting, diaphragm storage, or sanitary napkins: King, Pierce, and Snohomish counties, Washington State, 1986–1988

Type of powder	Ovarian cancer cases (n = 313)		Controls (n = 422)		RR*	95% CI*
	No	%	No	%		
Lifetime use (none)	154	49.2	256	60.7	1.0	Referent
Exclusive use of						
Talcum powder only	16	5.1	16	3.8	1.2†	0.6–2.5
Baby powder only	31	9.9	36	8.5	1.4†	0.8–2.4
Cornstarch only	5	1.6	11	2.6	0.9†	0.3–2.9
Deodorizing powder only	9	2.9	10	2.4	1.0†	0.4–2.6
Bath/body powder only	27	8.6	25	5.9	1.6†	0.9–3.0
Unspecified type only	11	3.5	4	0.9		
Use of‡						
Any talcum powder	33	10.5	23	5.5	1.6§	0.9–2.8
Any baby powder	52	16.6	61	14.5	1.1§	0.7–1.8
Any cornstarch	8	2.6	16	3.8	0.8§	0.3–2.0
Any deodorizing powder	24	7.7	24	5.7	1.1§	0.6–2.0
Any bath/body powder	52	16.6	43	10.2	1.5§	0.9–2.4
Any unspecified type	24	7.7	11	2.6		

* RR, relative risk; CI, confidence interval.

† Adjusted for age.

‡ Numbers do not add up to total cases and controls with any powder use because women may have used a variety of powders.

§ Adjusted for age and the other types of powders used (yes, no).

Few of the above factors studied showed any statistically significant difference between cases and controls. Of the 30 lines of data reported in tables 3 and 4, only 3 (10%) show a marginal statistical significance. Those include any perineal dusting (R.R. 1.6, C.I. 1.1–2.3), any genital deodorant spray (R.R. 1.9, C.I. 1.1–3.1), and any genital deodorant spray, cumulative lifetime months >12 (R.R. 2.7, C.I. 1.1–6.6). The remaining 27/30 rows of data demonstrate that both groups (cases vs controls) are similar, with confidence intervals that cross 1.0. There is no dose-response relationship. The authors note that the limitations of their study included selection bias, as a significant proportion of eligible women either declined to participate or died prior to being contacted. They also note that differential reporting of talc use between cases and controls (recall bias) could have impacted results and could be eliminated in future prospective cohort studies. As discussed in detail below, we now have four prospective cohort studies that show no association between genital talc use and ovarian cancer.

Ness et al. 2000⁹⁴ selected 2,418 cases of histologically confirmed ovarian cancer in Pennsylvania, New Jersey and Delaware; however, only 767 were interviewed. Of 2,314 households eligible to offer a participating control, only 1,367 ended up participating in the study. When comparing cases to controls, statistical significance again failed to materialize in many of the points that the authors studied. In Table 2 (p 114), points that failed to meet the standard for statistical significance include: < 1 year, 5–9 years and 10+ years of talc use. All of these had the C.I. cross 1.0.

⁹⁴ Ness, R. B., Grisso, J. A., Cottreau, C., Klapper, J., Vergona, R., Wheeler, J. E., ... & Schlesselman, J. J. (2000). Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology*, 11(2), 111–117.

The authors note that talc use (applied to any part of the body or to sanitary napkins) was associated with ovarian cancer risk.⁹⁵ However, even though talc use on a diaphragm places the talc immediately adjacent to the cervix, and talc use by a male partner has a similar if not more pronounced effect during coitus, no relationship was found between these two important factors and the risk of ovarian cancer. This also argues against the hypothesis of talc migration and its relationship to ovarian cancer. Notably, a history of PID did not increase the risk of ovarian cancer (O.R. 1.3, C.I. 0.6-2.5).

TABLE 2. Environmental Factors and Medical Conditions and Ovarian Cancer

Variable	Cases 767	Controls 1367	Crude OR	95% CI	Adjusted OR*	95% CI
Talc use†						
Never	349	728	1.0		1.0	
Feet, etc	335	512	1.4	1.1-1.6	1.4	1.1-1.6
Genital/rectal	161	219	1.5	1.2-1.9	1.5	1.1-2.0
Sanitary napkin	77	94	1.7	1.2-1.9	1.6	1.1-2.3
Underwear	70	100	1.5	1.0-2.0	1.7	1.2-2.4
Diaphragm/Cerv Cap	10	33	0.6	0.3-1.3	0.6	0.3-1.2
Male partner	56	126	0.9	0.7-1.3	1.0	0.7-1.4
Talc use (genital/rectal and feet)						
Never	401	819	1.0		1.0	
<1 year	17	17	2.0	1.0-4.0	2.0	1.0-4.0
1-4 years	76	101	1.5	1.1-2.1	1.6	1.1-2.3
5-9 years	40	59	1.4	0.9-2.1	1.2	0.8-1.9
10+ years	233	371	1.3	1.0-1.6	1.2	1.0-1.5
Ovarian cysts						
No	604	1131	1.0		1.0	
Yes	154	231	1.2	1.0-1.6	1.3	1.1-1.7
Thyroid disease						
Never	646	1165	1.0		1.0	
Overactive	30	30	1.8	1.1-3.0	1.8	1.0-3.0
Underactive	72	138	0.9	0.7-1.3	0.9	0.6-1.2
Endometriosis						
No	698	1279	1.0		1.0	
Yes	66	85	1.5	1.0-2.1	1.7	1.2-2.4
Pelvic inflammatory disease						
No	752	1335	1.0		1.0	
Yes	14	27	0.9	0.5-1.8	1.3	0.6-2.5

* Adjusted for age, number of pregnancies, family history of ovarian cancer, race, oral contraceptive use, tubal ligation, hysterectomy, and breast-feeding.
† Subjects may have used talc on more than one area of the body so numbers add to more than 767 cases and 1,367 controls.

Mills et al. 2004⁹⁶ studied women in Central California in a case-control fashion. 256 cases were compared to 1,122 controls chosen by random digit dialing with the selection bias noted above. Again, there was no dose-response relationship as noted in Table II (p 460):

TABLE II - FREQUENCIES, MULTIVARIATE-ADJUSTED ODDS RATIOS AND 95% CONFIDENCE INTERVALS FOR PATTERNS OF TALC USE FOR EOC CASES AND CONTROLS, CENTRAL VALLEY OF CALIFORNIA, 2000-2001

Patterns of talc use	Cases (%) (n = 256) ¹	Controls (%) (n = 1,122)	Multivariate-adjusted OR (95% CI)
Talc use			
Never	143 (57.4)	695 (62.9)	1.0
Ever	106 (42.6)	410 (37.1)	1.37 (1.02-1.85)
Frequency of use			
Never	143 (57.4)	695 (63.2)	1.0
Rarely to several times per month	34 (13.7)	138 (12.5)	1.34 (0.87-2.08)
1-3 times per week	31 (12.4)	145 (13.2)	1.16 (0.74-1.81)
4-7 times per week	41 (16.5)	122 (11.1)	1.74 (1.14-2.64)
			Trend p = 0.015
Duration of use			
Never	143 (58.9)	695 (64.2)	1.0 (referent)
≤ 3 years	18 (7.4)	99 (9.2)	1.01 (0.58-1.76)
4-12 years	32 (13.2)	98 (9.1)	1.86 (1.16-2.98)
13-30 years	29 (11.9)	102 (9.4)	1.45 (0.90-2.32)
> 30 years	21 (8.6)	88 (8.1)	1.22 (0.72-2.08)
			Trend p = 0.045
Cumulative use (frequency × duration)			
Never	143 (58.9)	695 (64.4)	1.0 (referent)
First quartile (lowest exposure)	18 (7.4)	95 (8.8)	1.03 (0.59-1.80)
Second quartile	28 (11.5)	95 (8.8)	1.81 (1.10-2.97)
Third quartile	34 (14.0)	107 (9.9)	1.74 (1.11-2.73)
Fourth quartile (highest exposure)	20 (8.2)	88 (8.1)	1.06 (0.62-1.83)
			Trend p = 0.051

Adjusted for age, race/ethnicity, duration of oral contraceptive use and breast feeding. ¹Numbers may not add up to total cases and controls due to missing data.

⁹⁵ Ness, R. B., Grisso, J. A., Cottreau, C., Klapper, J., Vergona, R., Wheeler, J. E., ... & Schlesselman, J. J. (2000). Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology*, 11(2), 111-117.

⁹⁶ Mills, P. K., Riordan, D. G., Cress, R. D., & Young, H. A. (2004). Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *International Journal of Cancer*, 112(3), 458-464.

Note in the table above that duration of use shows no significant difference for ≤ 3 years, 13-30 years, or > 30 years. The study does show a statistically significant difference for 4-12 years. In the “Cumulative use (frequency x duration)” section near the bottom of the table, there is no significant difference for the lowest exposure nor the highest exposure. There is a significant difference only for the second quartile and third quartile. If talcum powder were truly a carcinogen, we should see consistent dose-response relationships, similar to number of cigarettes smoked per day and the risk of lung cancer that Doll & Bradford Hill noted in 1950.⁹⁷ We simply do not see this important relationship.

Merritt et al. 2008⁹⁸ reported on 1,576 women with ovarian cancer who were participating in the Australian Ovarian Cancer Study and compared them to 1,509 controls. They found a “small but significantly increased risk of ovarian cancer”⁹⁹ with talc use (O.R. 1.17 C.I. 1.01-1.36) but no dose-response relationship with increasing duration of use (Table II, below).

	Controls ¹ N (%)	All cases ¹ N (%)	All cases (N = 1,576) OR ² (95% CI)	Serous (N = 994) OR ² (95% CI)	Mucinous (N = 191) OR ² (95% CI)	Endometrioid (N = 141) OR ² (95% CI)	Clear cell (N = 88) OR ² (95% CI)
Perineal use of talcum powder ³							
Never	835 (57)	821 (54)	1.0	1.0	1.0	1.0	1.0
Ever	635 (43)	702 (46)	1.17 (1.01-1.36)	1.21 (1.03-1.44)	1.10 (0.80-1.52)	1.18 (0.81-1.70)	1.08 (0.68-1.72)
Use pre- or no-surgery ³							
None	835 (57)	821 (54)	1.0	1.0	1.0	1.0	1.0
>0-10 years	193 (13)	200 (13)	1.13 (0.90-1.41)	1.26 (0.98-1.63)	0.79 (0.47-1.33)	1.05 (0.59-1.85)	1.08 (0.52-2.27)
>10-25 years	214 (15)	213 (14)	1.08 (0.87-1.34)	1.03 (0.80-1.32)	1.34 (0.86-2.08)	1.14 (0.67-1.94)	0.96 (0.48-1.90)
>25 years	228 (16)	289 (19)	1.29 (1.04-1.58)	1.34 (1.06-1.68)	1.21 (0.75-1.97)	1.31 (0.80-2.16)	1.18 (0.63-2.22)
p-Value (trend)			0.021	0.022	0.27	0.28	0.69
Use post-surgery							
None	1,294 (88)	1,340 (88)	1.0	1.0	1.0	1.0	1.0
>0-10 years	49 (3)	50 (3)	1.08 (0.71-1.62)	1.07 (0.67-1.69)	1.39 (0.60-3.19)	0.97 (0.34-2.77)	0.64 (0.15-2.81)
>10-25 years	81 (6)	87 (6)	1.14 (0.82-1.57)	1.03 (0.72-1.48)	2.04 (1.09-3.79)	1.03 (0.45-2.32)	0.44 (0.11-1.88)
>25 years	46 (3)	46 (3)	1.00 (0.64-1.51)	1.09 (0.69-1.71)	0.91 (0.27-3.05)	0.79 (0.23-2.64)	0.43 (0.06-3.22)
p-Value (trend)			0.61	0.60	0.12	0.81	0.16
Ever ² vs. never use stratified by age at diagnosis/recruitment							
<50 years	143 (23)	137 (20)	1.16 (0.86-1.57)	1.53 (1.06-2.19)	1.42 (0.89-2.25)	0.66 (0.28-1.55)	0.98 (0.41-2.29)
50-59 years	213 (33)	237 (34)	1.22 (0.93-1.59)	1.20 (0.89-1.62)	0.76 (0.46-1.26)	1.41 (0.78-2.54)	1.67 (0.88-3.15)
60-69 years	191 (30)	207 (29)	0.93 (0.70-1.23)	0.95 (0.70-1.29)	0.83 (0.49-1.40)	1.31 (0.62-2.75)	0.87 (0.40-1.85)
≥70 years	88 (14)	121 (17)	1.61 (1.10-2.36)	1.66 (1.08-2.56)	0.91 (0.42-1.97)	1.32 (0.50-3.49)	1.41 (0.58-3.35)

¹Numbers may not sum to total because of missing data. ²Adjusted for age (except age-stratified analysis), education, parity and oral contraceptive pill use. ³Analysis restricted to use while the genital tract was unobstructed (i.e., prior to hysterectomy).

Gates et al. 2008¹⁰⁰ analyzed specimens from a New England-based case-control study of 1,175 cases and 1,202 controls to assess whether the talc/ovarian cancer association is modified by variants of several genes. Importantly, as noted in Table 1, only 69 of the 1,175 cases (5.9%) and 63 of the 1,202 controls reported any use of talc (5.2%). Daily genital talc use was reported in only 34 of 1,175 cases (2.9%) and in 25 of 1,202 controls (2.1%). The authors in Gates note that in the NECC study, women with regular genital talc use were older, had higher mean BMI, were less likely to have used OCPs, were more likely to be

⁹⁷Doll, R., & Hill, A. B. (1950). Smoking and carcinoma of the lung. *British Medical Journal*, 2(4682), 739-748.

⁹⁸ Merritt, M. A., Green, A. C., Nagle, C. M., Webb, P. M., & Australian Cancer Study (Ovarian Cancer) and Australian Ovarian Cancer Study Group. (2008). Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *International Journal of Cancer*, 122(1), 170-176.

⁹⁹ Merritt, M. A., Green, A. C., Nagle, C. M., Webb, P. M., & Australian Cancer Study (Ovarian Cancer) and Australian Ovarian Cancer Study Group. (2008). Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *International Journal of Cancer*, 122(1), 170-176.

¹⁰⁰ Gates, M. A., Tworoger, S. S., Terry, K. L., Titus-Ernstoff, L., Rosner, B., De Vivo, I., ... & Hankinson, S. E. (2008). Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. *Cancer Epidemiology and Prevention Biomarkers*, 17(9), 2436-2444.

postmenopausal, and were more likely to have used HRT.¹⁰¹ These risk factors, which were higher in the talc use group, could potentially increase a woman's odds of developing ovarian cancer.

Kurta et al. 2012¹⁰² reported on the use of fertility drugs, studying their use in 902 ovarian cancer cases and comparing them to 1,802 controls who were identified via random digit dialing. Data were obtained from the Hormones and Ovarian Cancer Prediction (HOPE) study. The authors concluded that fertility drugs did not significantly contribute to ovarian cancer among the majority of women. A weak association between perineal talc use and ovarian cancer (O.R. 1.4, C.I. 1.16-1.69) was reported.¹⁰³

Wu et al. 2015¹⁰⁴ reported on the risk of ovarian cancer in African-Americans and Hispanics, comparing them to non-Hispanic Whites in Los Angeles County. (Note that Wu et al. 2015 captures the subset of data reported on in Pike 2004 and Wu et al. 2009.) The authors studied various potential risk factors in Hispanics (308 cases vs 380 controls), African-Americans (128 cases vs 143 controls), and Whites (1,265 cases vs 1,868 controls). Talc use was more common in African-American women.¹⁰⁵ When combining all races, they found a weak association of O.R. 1.46 (C.I. 1.27-1.69) between talc use and ovarian cancer, but this association did not occur in African-Americans, who had an O.R. of 1.15 (C.I. 0.90-1.47) for "per 5 years of talc use" and an O.R. 1.56 (C.I. 0.80-3.04) for "Yes" talc use.¹⁰⁶

Cramer et al. 2016¹⁰⁷ reported on the association of talc use and ovarian cancer in two US States. As noted earlier in this report, there was no dose-response noted. In fact, the O.R. for < 8 years used (O.R. 1.31, C.I. 1.03-1.68) was similar to that for > 35 years (O.R. 1.33, C.I. 1.03-1.71).¹⁰⁸ Cramer did find the p-value for the trend of years used to be significant, at $p < 0.002$; however, the odds ratios are extremely

¹⁰¹ Gates, M. A., Tworoger, S. S., Terry, K. L., Titus-Ernstoff, L., Rosner, B., De Vivo, I., ... & Hankinson, S. E. (2008). Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. *Cancer Epidemiology and Prevention Biomarkers*, 17(9), 2436-2444, 2439.

¹⁰² Kurta, M. L., Moysich, K. B., Weissfeld, J. L., Youk, A. O., Bunker, C. H., Edwards, R. P., ... & Diergaarde, B. (2012). Use of fertility drugs and risk of ovarian cancer: results from a US-based case-control study. *Cancer Epidemiology and Prevention Biomarkers*, 21(8), 1282-1292.

¹⁰³ Kurta, M. L., Moysich, K. B., Weissfeld, J. L., Youk, A. O., Bunker, C. H., Edwards, R. P., ... & Diergaarde, B. (2012). Use of fertility drugs and risk of ovarian cancer: results from a US-based case-control study. *Cancer Epidemiology and Prevention Biomarkers*, 21(8), 1286, Table 1.

¹⁰⁴ Wu, A. H., Pearce, C. L., Tseng, C. C., & Pike, M. C. (2015). African Americans and hispanics remain at lower risk of ovarian cancer than non-hispanic whites after considering nongenetic risk factors and oophorectomy rates. *Cancer Epidemiology and Prevention Biomarkers*, 24(7), 1094-1100.

¹⁰⁵ Wu, A. H., Pearce, C. L., Tseng, C. C., & Pike, M. C. (2015). African Americans and hispanics remain at lower risk of ovarian cancer than non-hispanic whites after considering nongenetic risk factors and oophorectomy rates. *Cancer Epidemiology and Prevention Biomarkers*, 24(7), 1096.

¹⁰⁶ Wu, A. H., Pearce, C. L., Tseng, C. C., & Pike, M. C. (2015). African Americans and hispanics remain at lower risk of ovarian cancer than non-hispanic whites after considering nongenetic risk factors and oophorectomy rates. *Cancer Epidemiology and Prevention Biomarkers*, 24(7), 1096.

¹⁰⁷ Cramer, D. W., Vitonis, A. F., Terry, K. L., Welch, W. R., & Titus, L. J. (2016). The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*, 27(3), 334-346.

¹⁰⁸ Cramer, D. W., Vitonis, A. F., Terry, K. L., Welch, W. R., & Titus, L. J. (2016). The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*, 27(3), 336, Table 1.

similar, as are the confidence intervals for each group of “years used.”¹⁰⁹ Cramer also pointed out that OCAC found an association with clear cell, but he did not.¹¹⁰ The Cramer study also contrasted with the results of the WHI study, “raising the issue of recall bias in case-control studies” per the authors.¹¹¹

Schildkraut et al. 2016¹¹² studied 584 cases and 745 controls who were enrolled in the “African American Cancer Epidemiology Study” (AACES). The cases were women with newly diagnosed epithelial ovarian cancer, and controls were identified through random digit phone dialing. There were several statistically significant differences between cases and controls. There was a significant difference in age ($p < 0.01$), education ($p 0.02$), tubal ligation ($p 0.02$), oral contraceptive use ($p < 0.01$), first-degree family member with breast or ovarian cancer ($p < 0.01$).¹¹³ One risk factor that increases one’s risk of developing ovarian cancer is family history of cancer; this was higher in cases than controls. Another risk factor is age, also higher in cases than controls. A history of using OCPs or having had a BTL was higher in controls and lower in cases. These differences between groups are referred to as confounding variables. These confounding variables could easily account for differences, resulting in skewed findings and conclusions based on differences between the groups. Also, the authors note in their discussion (p 1416): “The possibility of differential misclassification exists in a case control study such as AACES, especially due to the heightened awareness of the exposure as a result of two recent class action lawsuits.” While the authors attempted to reduce this bias by adjusting for the date of interview (before/after media publicity), they acknowledged that “there is still a possibility that recall bias may have caused some inflation of the ORs.”¹¹⁴

The table that is excerpted to the right, (Table 2. From the Schildkraut 2016 publication) demonstrates there was a significant difference between cancer cases (but not

<i>Interview date <2014</i>	<i>(n=351)</i>	<i>(n=571)</i>		
Never use	147 (41.9)	286 (48.4)	1.00	Referent
Only non-genital use	76 (21.7)	104 (17.6)	1.40	0.96,2.03
Any genital use	128 (36.5)	201 (34.0)	1.19	0.87,1.63
<i>Interview date ≥2014</i>	<i>(n=233)</i>	<i>(n=154)</i>		
Never use	70 (30.0)	65 (42.2)	1.00	Referent
Only non-genital use	43 (18.4)	36 (23.3)	1.26	0.69,2.32
Any genital use	120 (51.5)	53 (34.4)	2.91	1.70,4.97

controls) when looking at “Interview date < 2014” vs “Interview date \geq 2014.” The odds ratio for any genital talc use for Interview date < 2014 was 1.19 (C.I. 0.87-1.63), demonstrating that prior to 2014, there was no increased risk associated with any genital use of talcum powder. However, after 2014, there is a

¹⁰⁹ Cramer, D. W., Vitonis, A. F., Terry, K. L., Welch, W. R., & Titus, L. J. (2016). The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*, 27(3), 336, Table 1.

¹¹⁰ Cramer, D. W., Vitonis, A. F., Terry, K. L., Welch, W. R., & Titus, L. J. (2016). The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*, 27(3), 341.

¹¹¹ Cramer, D. W., Vitonis, A. F., Terry, K. L., Welch, W. R., & Titus, L. J. (2016). The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*, 27(3), 341.

¹¹² Schildkraut, J. M., Abbott, S. E., Alberg, A. J., Bandera, E. V., Barnholtz-Sloan, J. S., Bondy, M. L., ... & Schwartz, A. G. (2016). Association between body powder use and ovarian cancer: the African American Cancer Epidemiology Study (AACES). *Cancer Epidemiology and Prevention Biomarkers*, 25(10), 1411-1417.

¹¹³ Schildkraut, J. M., Abbott, S. E., Alberg, A. J., Bandera, E. V., Barnholtz-Sloan, J. S., Bondy, M. L., ... & Schwartz, A. G. (2016). Association between body powder use and ovarian cancer: the African American Cancer Epidemiology Study (AACES). *Cancer Epidemiology and Prevention Biomarkers*, 25(10), 1413, Table 1.

¹¹⁴ Schildkraut, J. M., Abbott, S. E., Alberg, A. J., Bandera, E. V., Barnholtz-Sloan, J. S., Bondy, M. L., ... & Schwartz, A. G. (2016). Association between body powder use and ovarian cancer: the African American Cancer Epidemiology Study (AACES). *Cancer Epidemiology and Prevention Biomarkers*, 25(10), 1416.

significant difference with O.R. 2.91 (C.I. 1.7-4.97), demonstrating the significant increase in recall bias after 2014.

Exposure	Cases (n=584) n (%)	Controls (n=745) n (%)	OR ^a	95% CI
Body powder use				
Never use	217 (37.2)	351 (47.1)	1.00	Referent
Ever use	367 (62.8)	394 (52.9)	1.39	1.10, 1.76
Body powder use by location				
Never use	217 (37.2)	351 (47.1)	1.00	Referent
Only non-genital use	119 (20.4)	140 (18.8)	1.31	0.95, 1.79
Any genital use	248 (42.5)	254 (34.1)	1.44	1.11, 1.86
Interview date <2014 (n=351)		(n=571)		
Never use	147 (41.9)	286 (48.4)	1.00	Referent
Only non-genital use	76 (21.7)	104 (17.6)	1.40	0.96, 2.03
Any genital use	128 (36.5)	201 (34.0)	1.19	0.87, 1.63
Interview date ≥2014 (n=233)		(n=154)		
Never use	70 (30.0)	65 (42.2)	1.00	Referent
Only non-genital use	43 (18.4)	36 (23.3)	1.26	0.69, 2.32
Any genital use	120 (51.5)	53 (34.4)	2.91	1.70, 4.97
Frequency of use				
Never use	217 (37.3)	351 (47.2)	1.00	Referent
Only non-genital use				
Less than daily	61 (10.5)	82 (11.0)	1.15	0.78, 1.71
Daily	58 (10.0)	58 (7.8)	1.53	1.00, 2.35
p-for-trend				0.09
Any genital use				
Less than daily	88 (15.1)	119 (16.0)	1.12	0.80, 1.58
Daily	158 (27.2)	134 (18.0)	1.71	1.26, 2.33
p-for-trend				<0.01
Duration of use				
Never use	217 (37.4)	351 (47.4)	1.00	Referent
Only non-genital use				
<20 years	59 (10.2)	68 (9.2)	1.37	0.91, 2.07
≥20 years	60 (10.3)	70 (9.5)	1.28	0.85, 1.93
p-for-trend				0.13
Any genital use				
<20 years	101 (17.4)	118 (15.9)	1.33	0.95, 1.86
≥20 years	144 (24.8)	134 (18.1)	1.52	1.11, 2.07
p-for-trend				0.02
Lifetime body powder applications				
Never use	217 (37.4)	351 (47.4)	1.00	Referent
Only non-genital use				
Below median (<3600 applications)	60 (10.3)	72 (9.7)	1.35	0.90, 2.03
Above median (≥3600 applications)	59 (10.2)	66 (8.9)	1.30	0.86, 1.97
p-for-trend				0.14
Any genital use				
Below median (<3600 applications)	92 (15.9)	119 (16.1)	1.16	0.83, 1.63
Above median (≥3600 applications)	152 (26.2)	133 (17.9)	1.67	1.23, 2.26
p-for-trend				<0.01

^a Adjusted for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of OC use, first degree family history of breast or ovarian cancer, and interview year.

Davis et al. 2021¹¹⁵ reported on data from the “Ovarian Cancer in Women of African Ancestry consortium” and found that ever use of genital powder and the O.R. of developing ovarian cancer was similar across race, even though powder use was more common in African-American women. Overall, in both African-American women and White women combined, there was an increased risk (O.R. 1.32, C.I. 1.17-1.48).

¹¹⁵ Davis, C. P., Bandera, E. V., Bethea, T. N., Camacho, F., Joslin, C. E., Wu, A. H., ... & Harris, H. R. (2021). Genital powder use and risk of epithelial ovarian cancer in the Ovarian Cancer in Women of African Ancestry Consortium. *Cancer Epidemiology and Prevention Biomarkers*, 30, 1660-1668.

However African-American women did not demonstrate an increased risk of developing ovarian cancer overall (O.R. 1.22, C.I. 0.97-1.53), and the data showed no dose-response. The risk of developing ovarian cancer did not vary by cancer histologic type. Eligibility for the analysis by Davis, et al. “was restricted to interview year prior to 2014 for case-control studies to reduce recall bias following the [] lawsuits that were filed in 2014.”¹¹⁶ Schildkraut, JM was a co-author of this study.

Prospective Cohort Studies

There have been 4 prospective cohort studies performed, including the Nurses’ Health Study, Nurses’ Health Study II, Sister Study and the Women’s Health Initiative Observational Study, none of which showed a statistically significant association between talcum powder and ovarian cancer. A pooled analysis of these four prospective cohort studies was published by O’Brien et al.¹¹⁷ and does not support an association between talc use and ovarian cancer. O’Brien subsequently published a manuscript in 2024 using artificial measures to manipulate the data which I address below in regards to the Sister Study.

Nurses’ Health Study (NHS) (Gertig et al., 2000¹¹⁸): This article by Gertig et al. published in 2000 was the first to report findings in the NHS I population of 121,700 nurses. The study was established in 1976 and followed these women for several decades. An updated analysis of the data was published by Gates et al. in 2010 and is detailed below. In the publication by Gertig et al., the authors found no statistically significant association between the use of talcum powder and the development of epithelial ovarian cancer (R.R. 1.09, C.I. 0.86-1.37). They did note an association between the “ever use” of talcum powder and the development of high grade serous ovarian cancer (R.R. 1.40, C.I. 1.02-1.91). However, when these women were followed for another decade, as reported by Gates et al. in 2010,¹¹⁹ this association disappeared.

Nurses’ Health Study (Gates et al., 2010¹²⁰): This study added to the follow-up of the original Nurses’ Health Study. As demonstrated in the table below, with an additional 10 years of follow-up data, there was no statistically significant association between the use of talcum powder and ovarian cancer generally or with any histologic subtype, including serous invasive (R.R. 1.06, C.I. 0.84-1.35).

¹¹⁶ Davis, C. P., Bandera, E. V., Bethea, T. N., Camacho, F., Joslin, C. E., Wu, A. H., ... & Harris, H. R. (2021). Genital powder use and risk of epithelial ovarian cancer in the Ovarian Cancer in Women of African Ancestry Consortium. *Cancer Epidemiology and Prevention Biomarkers*, 30, 1660-1668. (citing Schildkraut, JM et al. (2016)).

¹¹⁷ O’Brien, K. M., Tworoger, S. S., Harris, H. R., Anderson, G. L., Weinberg, C. R., Trabert, B., ... & Wentzensen, N. (2020). Association of powder use in the genital area with risk of ovarian cancer. *JAMA*, 323(1), 49-59.

¹¹⁸ Gertig, D. M., Hunter, D. J., Cramer, D. W., Colditz, G. A., Speizer, F. E., Willett, W. C., & Hankinson, S. E. (2000). Prospective study of talc use and ovarian cancer. *Journal of the National Cancer Institute*, 92(3), 249-252.

¹¹⁹ Gates, M. A., Rosner, B. A., Hecht, J. L., & Tworoger, S. S. (2010). Risk factors for epithelial ovarian cancer by histologic subtype. *American Journal of Epidemiology*, 171(1), 45-53.

¹²⁰ Gates, M. A., Rosner, B. A., Hecht, J. L., & Tworoger, S. S. (2010). Risk factors for epithelial ovarian cancer by histologic subtype. *American Journal of Epidemiology*, 171(1), 45-53.

Table 4. Association Between Nonreproductive Exposures and Risk of Epithelial Ovarian Cancer, by Histologic Subtype, Among 108,446 Women in the NHS From 1976 to 2006 and 112,054 Women in the NHSII From 1989 to 2005^a

	All Epithelial (n = 876)		Serous Invasive (n = 468)		Endometrioid (n = 134)		Mucinous ^b (n = 84)		P-Heterogeneity ^c
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	
Body mass index (per 5-kg/m ² increase)	1.05	0.98, 1.12	0.97	0.88, 1.07	1.18	1.02, 1.38	0.90	0.72, 1.13	0.06
Activity (per 15-MET-hour/week increase) ^d	1.05	0.98, 1.13	1.08	0.98, 1.19	0.94	0.76, 1.16	0.82	0.61, 1.10	0.11
Talc use (≥once/week vs. <once/week) ^e	1.06	0.89, 1.28	1.06	0.84, 1.35	1.06	0.66, 1.69	1.50	0.84, 2.66	0.55
Past smoker	1.05	0.91, 1.22	1.09	0.89, 1.34	0.59	0.39, 0.90	1.54	0.94, 2.53	0.03
Current smoker	1.11	0.92, 1.35	1.14	0.88, 1.49	0.93	0.59, 1.47	1.52	0.85, 2.74	
Family history of breast cancer	1.29	1.07, 1.56	1.34	1.04, 1.73	1.94	1.24, 3.03	1.42	0.76, 2.63	0.38
Family history of ovarian cancer ^f	1.75	1.19, 2.57	1.85	1.13, 3.03	0.47	0.07, 3.39	4.50	1.76, 11.51	0.06

Abbreviations: CI, confidence interval; MET, metabolic equivalent task; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RR, incidence rate ratio.

^a Estimates were adjusted for all variables in the table, plus all covariates in the final reproductive model (Table 2) and variables for missing data on talc use or family history of ovarian cancer (yes/no).

^b Includes borderline and invasive tumors.

^c P value from likelihood ratio test comparing, for each covariate, the model with separate estimates for the serous invasive, endometrioid, and mucinous histologic subtypes with the model with a single estimate across the 3 subtypes.

^d Cumulative average physical activity beginning in 1986 for the NHS and 1989 for the NHSII.

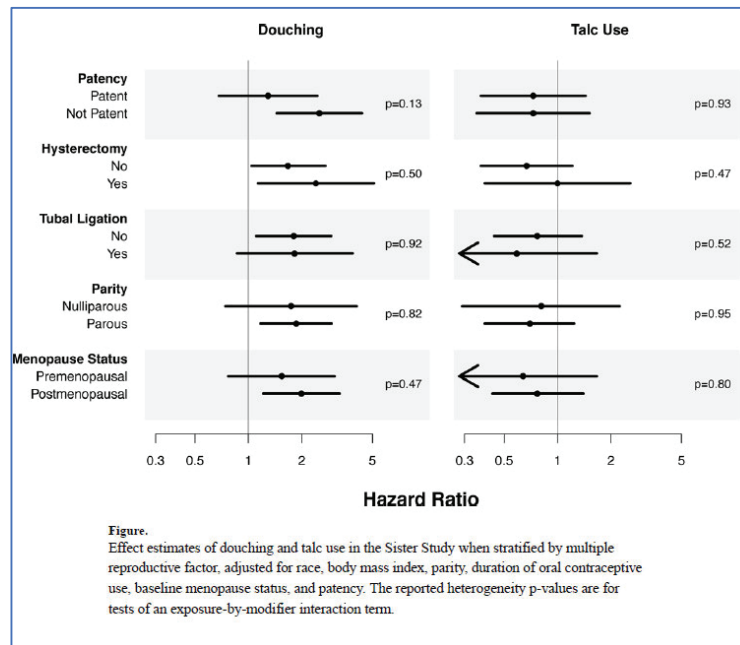
^e Information on regular genital talc use available for NHS participants only; collected in 1982.

^f Information on family history of ovarian cancer first collected in 1992 in the NHS and 1993 in the NHSII.

Am J Epidemiol 2010;171:45–53

Sister Study (Gonzalez et al., 2016¹²¹): Enrolled and followed 50,884 women who reported having a sister with breast cancer. Participants were asked about douching and talcum powder use at baseline. During follow-up, 154 women developed ovarian cancer. Douching was found to be more common among talc users, and douching was also associated with an increased risk of developing ovarian cancer (H.R. 1.9, C.I. 1.2-2.8). There was no association between the perineal application of talcum powder and the development of ovarian cancer (H.R. 0.73, C.I. 0.44-1.2). The lack of an association between the use of talcum powder and ovarian cancer is demonstrated in the graph below from the publication of Gonzalez et al.:

¹²¹ Gonzalez, N. L., O'Brien, K. M., D'Aloisio, A. A., Sandler, D. P., & Weinberg, C. R. (2016). Douching, talc use, and risk of ovarian cancer. *Epidemiology*, 27(6), 797-802.



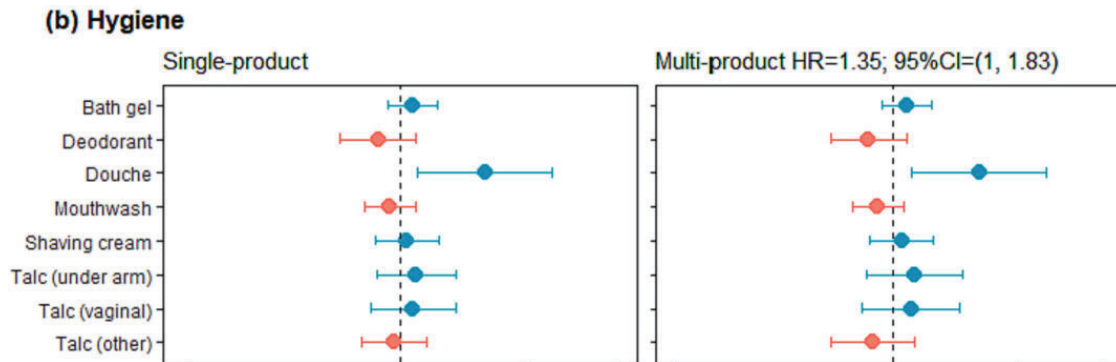
Sister Study:

Chang et al. published additional analyses of the data from the Sister Study in November 2024 with O'Brien as a co-author.¹²² They analyzed personal care product mixtures and incident hormone sensitive cancers. The authors reported a weak association between “hygiene mixture” and ovarian cancer (HR 1.35, 95% CI = 1.00-1.83). What they failed to include in their primary publication were several tables published as a supplement that found no association between genital talc use, hygiene products, and ovarian cancer.

Supplemental Tables demonstrate a weak association between hygiene products and ovarian cancer H.R. 1.36 (C.I. 1.00 - 1.85)¹²³ however this association disappeared when talc was analyzed as demonstrated in the figure 4 from the Chang paper shown below.

¹²² Chang, C.J., O'Brien K., Keil A., Goldberg M., Taylor K., Sandler D, White A. (2024). Use of personal care product mixtures and incident hormone-sensitive cancers in the Sister Study: A U.S.-wide prospective cohort. *Environment International*, 183:108298.

¹²³ Chang, C.J., O'Brien K., Keil A., Goldberg M., Taylor K., Sandler D, White A. (2024). Use of personal care product mixtures and incident hormone-sensitive cancers in the Sister Study: A U.S.-wide prospective cohort – Supplementary Tables. *Environment International*, 183:108298.



O'Brien et al published an analysis from the Sister Study earlier this month that attempted to mix both prospective and retrospective data, using both exposure data from enrollment (2003-2009) and data from a follow-up (2017-2019) questionnaire. Although the purpose of the study was to answer questions about potentially missing data, the new paper raises more questions than it answers. This is so because the follow-up questionnaire had substantial missing data as well as contradictory data. As a result, the authors used corrections and imputations to derive their risk ratios. "For ever versus never use analyses, we compared four possible scenarios using quantitative bias analysis: (1) no correction; (2) contradictory data correction; (3) contradictory data correction plus categorizing missing or undefined as exposed; and (4) contradictory data correction with multiple imputation of missing or undefined data." Each of these "assumptions" actually changed the data in the study and were applied to four different artificial scenarios. While O'Brien et al (2024) found an association between perineal talc use and ovarian cancer when applying artificial scenarios, their findings are not consistent with the totality of the epidemiological data or with the actual non-imputed data from the Sister Study. In my opinion, the results of the prospective cohort trials are clear and the data are overwhelming. Injecting assumptions and scenarios in order to change the data and the outcome of studies that have been peer reviewed and published cannot change the foundational conclusion that talcum powder applied to the female perineum does not cause ovarian cancer. To their credit, the authors do agree that "These results do not establish causality and do not implicate any specific cancer-inducing agent."

S-4

Product	Breast cancer				Ovarian cancer			
	Person-time	Non-case/case n	Weight (%) ^a	Adjusted HR (95%CI) from underlying models ^b	Person-time	Non-case/case n	Weight (%) ^a	Adjusted HR (95%CI) from underlying models ^b
Beauty	549283	43052/4036			453436	38403/264		
Blush			8.4	1.01 (0.98, 1.04)			-6	0.97 (0.88, 1.08)
Eyeliners			5.8	1.01 (0.99, 1.03)			-24.3	0.90 (0.82, 0.98)
Eye shadow			-49	0.96 (0.94, 0.99)			-12.9	0.94 (0.85, 1.05)
Foundation			12.5	1.02 (0.99, 1.04)			3.7	1.02 (0.93, 1.12)
Lip stick			-4.3	1.00 (0.97, 1.02)			8.8	1.05 (0.94, 1.16)
Mascara			15	1.02 (0.99, 1.05)			-9.7	0.96 (0.87, 1.06)
Makeup remover			-6.2	0.99 (0.97, 1.02)			18.5	1.10 (1.01, 1.21)
Perfume			4.8	1.01 (0.98, 1.03)			6.7	1.04 (0.94, 1.14)
Artificial nail			26.5	1.04 (0.98, 1.09)			7.7	1.04 (0.85, 1.27)
Cuticle cream			11.9	1.02 (0.98, 1.06)			9	1.05 (0.90, 1.22)
Nail polish			-40.5	0.97 (0.90, 1.05)			-47.1	0.81 (0.59, 1.12)
Nail polish remover			15.1	1.02 (0.94, 1.11)			45.6	1.27 (0.90, 1.79)
Hygiene	559255	43888/4109			461152	39092/267		
Bath gel			-7.4	1.00 (0.98, 1.02)			9.4	1.05 (0.97, 1.13)
Deodorant			47.6	1.03 (1.00, 1.07)			-41.2	0.93 (0.82, 1.05)
Douche			-0.1	1.00 (0.93, 1.07)			57.6	1.33 (1.06, 1.65)
Mouthwash			18.7	1.01 (0.99, 1.03)			-24.8	0.95 (0.88, 1.04)
Shaving cream			32.9	1.02 (0.99, 1.05)			6	1.03 (0.93, 1.14)
Talc (under arm)			-56.1	0.97 (0.93, 1.01)			14.7	1.07 (0.92, 1.26)
Talc (vaginal)			0.8	1.00 (0.96, 1.04)			12.3	1.06 (0.91, 1.24)
Talc (other)			-36.4	0.98 (0.95, 1.01)			-34	0.94 (0.82, 1.08)

S-5

Product	Breast cancer ^a				Ovarian cancer ^a			
	Age-adjusted HR (95%CI) ^b	<i>p</i> ^c	Fully adjusted HR (95%CI) ^{b,d}	<i>p</i> ^c	Age-adjusted HR (95%CI) ^b	<i>p</i> ^c	Fully adjusted HR (95%CI) ^{b,d}	<i>p</i> ^c
Hygiene								
Bath gel	1.00 (0.98, 1.02)	0.99	1.00 (0.98, 1.02)	0.89	1.06 (0.98, 1.14)	0.72	1.04 (0.96, 1.13)	0.86
Deodorant	1.04 (1.01, 1.08)	0.21	1.03 (1.00, 1.07)	0.45	0.96 (0.85, 1.08)	0.93	0.93 (0.82, 1.05)	0.86
Douche	1.00 (0.94, 1.07)	0.96	1.00 (0.94, 1.07)	0.98	1.37 (1.12, 1.68)	0.10	1.31 (1.06, 1.63)	0.46
Mouthwash	1.01 (0.99, 1.03)	0.49	1.01 (0.99, 1.04)	0.45	0.98 (0.91, 1.07)	0.95	0.97 (0.89, 1.05)	0.86
Shaving cream	1.02 (0.99, 1.05)	0.35	1.02 (0.99, 1.05)	0.45	1.03 (0.93, 1.14)	0.93	1.02 (0.92, 1.13)	0.86
Talc (under arm)	0.96 (0.92, 0.99)	0.21	0.96 (0.92, 0.99)	0.35	1.07 (0.94, 1.21)	0.84	1.05 (0.93, 1.19)	0.86
Talc (vaginal)	0.99 (0.95, 1.02)	0.72	0.98 (0.94, 1.01)	0.45	1.07 (0.94, 1.23)	0.84	1.04 (0.91, 1.19)	0.86
Talc (other)	0.98 (0.95, 1.01)	0.35	0.97 (0.94, 1.00)	0.35	1.01 (0.91, 1.12)	0.99	0.98 (0.88, 1.09)	0.86

As demonstrated in the tables above, the only statistically significant association identified by the study authors was for douching.

Women's Health Initiative (WHI) Observational Study (Houghton et al., 2014¹²⁴): The WHI enrolled 93,676 women from 40 centers around the United States. Women were 50-79 at enrollment, which is an enriched population to study ovarian cancer due to the advanced age of the study population. After exclusion criteria, the population for this report included 61,576 participants with 429 cases of ovarian cancer developed over a mean of 12.4 years. There was no association between the use of talcum powder

¹²⁴ Houghton, S. C., Reeves, K. W., Hankinson, S. E., Crawford, L., Lane, D., Wactawski-Wende, J., ... & Sturgeon, S. R. (2014). Perineal powder use and risk of ovarian cancer. *JNCI: Journal of the National Cancer Institute*, 106(9).

and the development of ovarian cancer. The authors analyzed potential association with powder use on genitals, powder use on sanitary napkins, powder use on diaphragm and combined ever powder use. None of these types of application was found to have any association with the development of ovarian cancer. The findings of the authors are detailed in the tables below:

Table 2. Age and multivariable-adjusted hazard ratios of ovarian cancer by area of perineal powder application (n = 61576): Women's Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR		Multivariable HR*	
			(95% CI)	<i>P</i> _{trend} †	(95% CI)	<i>P</i> _{trend} †
Powder use on genitals						
Never	247	457 855	1.0 (referent)	.63	1.0 (referent)	.67
Ever‡	181	304 867	1.13 (0.93 to 1.37)		1.12 (0.92 to 1.36)	
Less than 9 years	112	173 118	1.24 (0.99 to 1.55)		1.23 (0.98 to 1.54)	
10 or more years	68	129 647	0.98 (0.75 to 1.29)		0.98 (0.75 to 1.29)	
Powder use on sanitary napkins						
Never	336	590 351	1.0 (referent)	.70	1.0 (referent)	.69
Ever‡	93	172 712	0.96 (0.76 to 1.21)		0.95 (0.76 to 1.20)	
Less than 9 years	62	114 305	0.98 (0.75 to 1.28)		0.96 (0.73 to 1.26)	
10 or more years	30	56 174	0.93 (0.64 to 1.35)		0.95 (0.65 to 1.37)	
Powder use on diaphragm						
Never	373	661 239	1.0 (referent)	.78	1.0 (referent)	.67
Ever‡	52	97 714	0.94 (0.70 to 1.25)		0.92 (0.68 to 1.23)	
Less than 9 years	35	67 468	0.93 (0.66 to 1.32)		0.91 (0.64 to 1.30)	
10 or more years	17	29 202	0.99 (0.61 to 1.60)		0.95 (0.58 to 1.56)	
Combined ever powder use§						
Never	197	361 583	1.0 (referent)	.67	1.0 (referent)	.77
Ever‡	232	404 983	1.07 (0.89 to 1.30)		1.06 (0.87 to 1.28)	
Less than 9 years	135	228 931	1.12 (0.90 to 1.39)		1.09 (0.88 to 1.36)	
10 or more years	97	173 307	1.03 (0.81 to 1.31)		1.02 (0.80 to 1.30)	

* Adjusted for: Age (continuous), race (white, nonwhite, missing), oral contraceptive duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), hormone replacement therapy duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), family history (yes, no, missing), age (y) at last birth (never, <20, 20 to <30, 30+, missing), body mass index in kg/m² (<25.0, 25.0 to <30.0, 30.0+, missing), smoking (never, past, current, missing), tubal ligation (yes, no, missing), and parity (0, 1 to 2, 3 to 4, 5+, children, missing).

† Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in cox proportional hazard regression models; *P*_{trend} was estimated by modeling categories as continuous. All statistical tests were two-sided.

‡ Person-years may not add up; duration information was missing for some.

§ Combined ever powder use is the longest duration of use among the applications to genitals, sanitary napkins, and diaphragms.

Table 3. Age and multivariable-adjusted hazard ratios for ovarian cancer by combined categories of powder use (n = 61576): Women's Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR*	Multivariable HR*
			(95% CI)	(95% CI)
Powder Type Used				
No powder	193	355 523	1.0 (referent)	1.0 (referent)
Only genital powder	96	158 130	1.14 (0.90 to 1.46)	1.13 (0.88 to 1.45)
Only diaphragm powder	19	42 367	0.82 (0.51 to 1.32)	0.80 (0.50 to 1.29)
Only sanitary napkin powder	28	50 051	1.04 (0.70 to 1.54)	1.01 (0.68 to 1.50)
Genital and sanitary napkin powder	55	96 173	1.09 (0.80 to 1.47)	1.08 (0.80 to 1.46)
Genital and diaphragm powder	24	29 858	1.49 (0.98 to 2.28)	1.45 (0.95 to 2.23)
Diaphragm and sanitary napkin powder	4	68 58	1.06 (0.40 to 2.86)	1.02 (0.38 to 2.74)
Genital, diaphragm, and sanitary napkin powder	5	18 331	0.51 (0.21 to 1.24)	0.50 (0.21 to 1.22)

* Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in cox proportional hazard regression models. All statistical tests were two-sided. Multivariable HR adjusted for: age (continuous), race (white, nonwhite, missing), oral contraceptive duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), hormone replacement therapy duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), family history (yes, no, missing), age (y) at last birth (never, <20, 20 to <30, 30+, missing), body mass index in kg/m² (<25.0, 25.0 to <30.0, 30.0+, missing), smoking (never, past, current, missing), tubal ligation (yes, no, missing), and parity (0, 1 to 2, 3 to 4, 5+, children, missing).

Table 4. Age and multivariable-adjusted hazard ratios for combined ever powder use by subtype of ovarian cancer (n = 61 576): Women's Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR*	Multivariable HR*
			(95% CI)	(95% CI)
Serous†				
Never	87	355 523	1.0 (referent)	1.0 (referent)
Ever	117	404 983	1.18 (0.89 to 1.56)	1.16 (0.88 to 1.53)
Serous Invasive				
Never	80	355 523	1.0 (referent)	1.0 (referent)
Ever	105	404 983	1.16 (0.87 to 1.55)	1.13 (0.84 to 1.51)
Mucinous				
Never	12	355 523	1.0 (referent)	1.0 (referent)
Ever	13	404 983	0.98 (0.44 to 2.14)	1.03 (0.47 to 2.27)
Endometrioid				
Never	13	355 523	1.0 (referent)	1.0 (referent)
Ever	20	404 983	1.39 (0.69 to 2.79)	1.29 (0.64 to 2.61)
Other				
Never	47	355 523	1.0 (referent)	1.0 (referent)
Ever	54	404 983	1.04 (0.71 to 1.54)	1.04 (0.70 to 1.54)

* Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in cox proportional hazard regression models. All statistical tests were two-sided. Multivariable HR adjusted for: age (continuous), race (white, nonwhite, missing), oral contraceptive duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), hormone replacement therapy duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), family history (yes, no, missing), age (y) at last birth (never, <20, 20 to <30, 30+, missing), body mass index in kg/m² (<25.0, 25.0 to <30.0, 30.0+, missing), smoking (never, past, current, missing), tubal ligation (yes, no, missing), and parity (0, 1 to 2, 3 to 4, 5+, children missing).

† Includes borderline cancers.

Not one data point in the above tables shows any statistical association between the use of talcum powder and the development of ovarian cancer.

O'Brien et al. pooled the updated data from these prospective cohort studies, including data from the Nurses' Health Study II, and published their findings in 2020.¹²⁵ They noted that there were more than 250,000 women studied with a median age at baseline of 57, with 38% reporting genital powder use. Of these women, 10% reported long-term use. There was no association between the use of talcum powder and ovarian cancer with 3.8 million person-years at risk. "When the outcome was limited to medically confirmed cases, the HR was attenuated (Table 4; HR 1.05 [95% CI, 0.96 to 1.16] for ever use vs never use). There were no notable differences in estimates by invasive status, tumor location, or histologic subtype."¹²⁶ This is a powerful summary of the prospective data. Analyses were also stratified by numerous subgroups, including tubal ligation and patency. Although women with a patent reproductive tract had a slightly increased risk with ever use (HR=1.13, 95% CI 1.01-1.26), this HR did not differ significantly from women who did not have a patent reproductive tract (HR=0.99, 95% CI 0.86-1.15). As noted by Dr. Gossett in an editorial, the "subgroup analysis suggesting that women with intact reproductive tracts who used powder in the perineal area developed ovarian cancer more frequently than nonusers is below the effect size that epidemiologists generally consider important and should not be selectively highlighted by the statistically unsophisticated reader as evidence of a relationship."¹²⁷

¹²⁵ O'Brien, K. M., Tworoger, S. S., Harris, H. R., Anderson, G. L., Weinberg, C. R., Trabert, B., ... & Wentzensen, N. (2020). Association of powder use in the genital area with risk of ovarian cancer. *JAMA*, 323(1), 49-59.

¹²⁶ O'Brien, K. M., Tworoger, S. S., Harris, H. R., Anderson, G. L., Weinberg, C. R., Trabert, B., ... & Wentzensen, N. (2020). Association of powder use in the genital area with risk of ovarian cancer. *JAMA*, 323(1), 56.

¹²⁷ Gossett, D.R., del Carmen, M.G. (2020). Use of Powder in the Genital Area and Ovarian Cancer Risk: Examining the Evidence. *JAMA*, 323(1), 29-31.

Dr. Wolf questions whether these data are adequately powered; however, this concern was addressed by Berge et al., who determined that there is in fact adequate power to conclude that there is no association between the use of talcum powder and ovarian cancer.^{128, 129} Narod et al. suggest that a prospective study of more than 200,000 women studied for 10+ years would be needed to detect a significant association if the true OR is 1.2.¹³⁰ The O'Brien et al. 2020 publication meets this threshold posed by Narod et al.

In summary, the prospective cohort studies provide powerful insight as to cause and effect. There is strong consistency in the data. When looking at the sum of the data after completing all long-term follow-up, there is no data point which shows any association between talcum powder use and ovarian cancer.

Is Race a Factor:

As demonstrated in the table below, ovarian cancer is more common among Caucasian women compared to other races.¹³¹

Table 2
Descriptive characteristics of microscopically confirmed ovarian cancer cases, SEER 1992–1999^a

Classification	N	% ^b	Age (median)	Age distribution (%)			Racial distribution (%)				Stage of disease at diagnosis ^c (%)			
				<30	30–59	≥60	White	Black	Other	Unknown	Localized	Regional	Distant	Unstaged
All ovarian cancer	23,484	100.0	60.0	5.0	43.1	51.9	85.3	6.4	7.7	0.5	26.8	10.6	59.2	3.5
All epithelial	22,378	95.3	61.0	3.5	43.3	53.2	85.9	6.0	7.6	0.5	25.7	10.4	60.6	3.3
Serous	9734	41.4	60.0	4.2	45.1	50.7	87.3	6.1	6.1	0.6	22.2	9.1	67.0	1.7
Mucinous	3229	13.7	52.0	8.8	54.3	36.9	82.7	6.0	10.7	0.6	63.0	9.8	25.3	1.9
Endometrioid	2997	12.8	58.0	1.1	52.5	46.4	86.0	5.0	8.5	0.5	29.8	19.8	48.5	1.9
Clear cell	892	3.8	55.0	0.6	61.5	37.9	80.9	3.9	14.8	0.3	36.2	20.9	41.7	1.2
Other epithelial	5526	23.5	70.0	1.1	25.5	73.4	85.9	6.9	6.7	0.4	6.2	6.3	79.6	7.9
Germ cell	614	2.6	26.0	58.0	32.6	9.4	74.8	12.1	12.5	0.7	54.2	15.0	28.7	2.1
Sex cord-stromal	293	1.2	50.0	12.3	57.3	30.4	70.0	21.8	7.5	0.7	57.3	15.0	22.2	5.5
Other ovary	199	0.8	70.0	3.5	28.2	68.3	80.9	11.6	7.0	0.5	14.6	5.5	49.2	30.7

^a Surveillance, Epidemiology, and End Results (SEER) 11 registries program data, 1992–1999.

^b Percentage of 23,484 microscopically confirmed ovarian cancer cases.

^c Localized—cancer confined entirely to the ovary; Regional—cancer has extended into surrounding organs or tissues and/or regional lymph nodes; Distant—cancer has spread to parts of the body remote from the ovary; Unstaged—insufficient information to assign a stage.

As discussed above, a study by Davis et al. published in 2021 found no statistically significant increase in ovarian cancer in ever users of genital powder among African-American women (OR=1.22, 95% CI 0.97-1.53). This was despite the fact that powder use was higher among African-American women. The authors concluded that the differences in the risk of ovarian cancer between White and African-American women are not being driven by powder use.¹³²

¹²⁸ Amended Rule 26 Expert Report of Judith Wolf, MD dated November 15, 2023, p.6.

¹²⁹ Berge, W., Mundt, K., Luu, H., & Boffetta, P. (2018). Genital use of talc and risk of ovarian cancer: a meta-analysis. *European Journal of Cancer Prevention*, 27(3), 248-257.

¹³⁰ Narod, S. A. (2016). Talc and ovarian cancer. *Gynecologic Oncology*, 141(3), 410-412.

¹³¹ Quirk, J. T., & Natarajan, N. (2005). Ovarian cancer incidence in the United States, 1992–1999. *Gynecologic Oncology*, 97(2), 519-523.

¹³² Davis, C. P., Bandera, E. V., Bethea, T. N., Camacho, F., Joslin, C. E., Wu, A. H., ... & Harris, H. R. (2021). Genital powder use and risk of epithelial ovarian cancer in the Ovarian Cancer in Women of African Ancestry Consortium. *Cancer Epidemiology and Prevention Biomarkers*, 30, 1660-1668.

Meta-Analyses

There have been a number of meta-analyses published on the proposed association between talcum powder and ovarian cancer. Meta-analyses combine similar studies that meet specified methodologic standards. When one combines a group of data that was collected in a biased manner (selection bias, recall bias, observer/author bias, etc.) and analyzes it in a meta-analysis, then the biases can be amplified. Discussed below are the three most recently published meta-analyses.

Taher et al.¹³³ published in 2019 a meta-analysis of 27 studies. They included at least one study (Wu et al., 2009¹³⁴) that included duplicative study patient populations. For example, Wu et al. 2015 and Wu et al. 2009 were both included in Taher's analysis (see Table 1, Page 90). Including both of these Wu publications using the same set of patients would skew Taher's results. Taher et al. found a positive association between ovarian cancer and talc use (O.R.: 1.28, CI: 1.20-1.37). The authors used a GRADE framework, which describes the quality of the underlying evidence on talc and ovarian cancer as "very low certainty," meaning the "true effect is probably markedly different from the estimated effect."¹³⁵

Table 4
GRADE Pro Summary of Findings for Human Studies^a.

Outcomes	Anticipated absolute effects ^b (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with non-use	Risk with perineal use of talc			
Ovarian cancer	64 per 1000	80 per 1000 (75 to 85)	OR 1.28 (1.20 to 1.37)	15,303 cases 199,144 controls (27 observational studies)	VERY LOW^{c,d}

Additionally, the authors note (p 96) that the risk at the lowest exposure level in the Nurses' Health Study was "numerically, although not significantly, elevated." The data from the Nurses' Health Study actually showed no statistically significant difference (O.R. 1.15, C.I. 0.89-1.47).¹³⁶ Taher et al. refer to their Fig 3 as showing a "possible increasing trend in ovarian cancer risk with increasing cumulative exposure to talc" when there actually is no trend, as shown below in their figure:

¹³³ Taher, M. K., Farhat, N., Karyakina, N. A., Shilnikova, N., Ramoju, S., Gravel, C. A., ... & Krewski, D. (2019). Critical review of the association between perineal use of talc powder and risk of ovarian cancer. *Reproductive Toxicology*, 90, 88-101.

¹³⁴ Wu, A. H., Pearce, C. L., Tseng, C. C., Templeman, C., & Pike, M. C. (2009). Markers of inflammation and risk of ovarian cancer in Los Angeles County. *International Journal of Cancer*, 124(6), 1409-1415.

¹³⁵ Taher, M. K., Farhat, N., Karyakina, N. A., Shilnikova, N., Ramoju, S., Gravel, C. A., ... & Krewski, D. (2019). Critical review of the association between perineal use of talc powder and risk of ovarian cancer. *Reproductive Toxicology*, 90, 88-101.

¹³⁶ Barnard, M. E., Poole, E. M., Curhan, G. C., Eliassen, A. H., Rosner, B. A., Terry, K. L., & Tworoger, S. S. (2018). Association of analgesic use with risk of ovarian cancer in the Nurses' Health Studies. *JAMA oncology*, 4(12), 1675-1682.

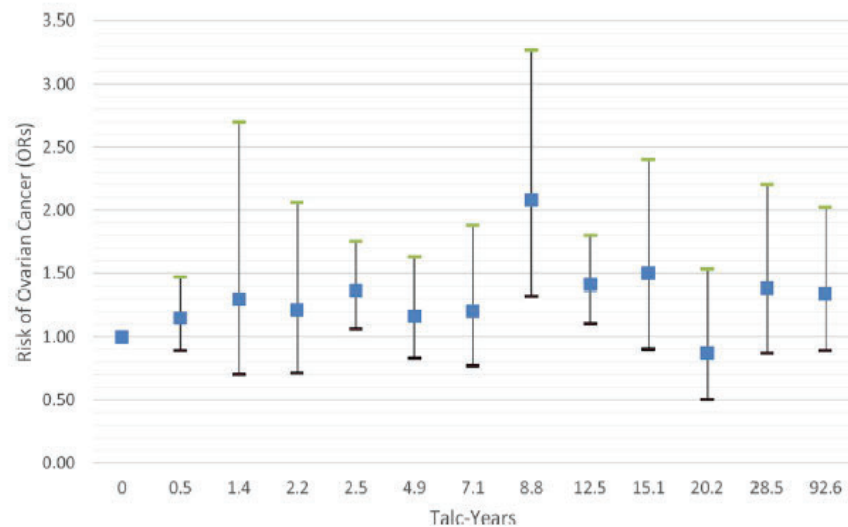


Fig. 3. Ovarian cancer risk estimates at increasing levels of exposure to talc, as reported from multiple studies.

Penninkilampi & Eslick 2018¹³⁷ published a meta-analysis of 24 case-control studies and 3 cohort studies. They note in their methods (p 42) a “systematic search” of the literature with searches of multiple databases with search terms like “talc” and “ovarian cancer.” The study, however, failed to include Gates et al. 2010,¹³⁸ which added 10 years of follow-up data to the Nurses’ Health Study analysis published by Gertig et al. 2000.¹³⁹ As noted above, Gertig et al. 2000 detected a slight increased risk of serous ovarian cancer that did not hold up with ten more years of follow-up as reported by Gates et al. 2010. In Gates, there was no significantly increased risk of ovarian cancer for any subtype, nor when all subtypes were combined.

Berge et al 2018¹⁴⁰ published a meta-analysis of the case-control studies as well as the cohort studies. The authors reported a relative risk of 1.26 (95% CI: 1.17-1.35) for the case-control studies. The cohort studies did not show an association, with a relative risk of 1.02 (95% CI: 0.85-1.29). The authors noted that the association present in the case-control studies can be attributed to bias in the case-control studies, including selection bias and information bias (recall bias). Berge also noted a “modest association between both duration and frequency of use of talc” but cautioned that the number of studies was not very large and “may reflect a true relationship, or recall bias or confounding, and analyses based on larger datasets would be required” (p 254). They also point out the lack of a dose-response relationship. Berge et al. did a statistical power analysis of the cohort studies in order to determine if they were adequately

¹³⁷ Penninkilampi, R., & Eslick, G. D. (2018). Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. *Epidemiology*, 29(1), 41-49.

¹³⁸ Gates, M. A., Rosner, B. A., Hecht, J. L., & Tworoger, S. S. (2010). Risk factors for epithelial ovarian cancer by histologic subtype. *American Journal of Epidemiology*, 171(1), 45-53.

¹³⁹ Gertig, D. M., Hunter, D. J., Cramer, D. W., Colditz, G. A., Speizer, F. E., Willett, W. C., & Hankinson, S. E. (2000). Prospective study of talc use and ovarian cancer. *Journal of the National Cancer Institute*, 92(3), 249-252.

¹⁴⁰ Berge, W., Mundt, K., Luu, H., & Boffetta, P. (2018). Genital use of talc and risk of ovarian cancer: a meta-analysis. *European Journal of Cancer Prevention*, 27(3), 248-257.

powered to detect a difference. They concluded that “low power cannot be invoked as [an] explanation for heterogeneity of results.”

Woolen et al. 2021 published a meta-analysis of 10 case-control studies and one cohort study, many of which were included in the meta-analyses mentioned above. Woolen reported an association between talcum powder use and ovarian cancer, noting “Frequent talcum powder use was associated with an elevated risk of ovarian cancer (adjusted pooled summary odds ratio 1.47 (95% CI 1.31, 1.65, $P < 0.0001$).” Of the 11 studies, 5/11 were statistically similar, with odds ratios that crossed one. Woolen actually states: “The possibility of additional confounders likely exists.”¹⁴¹ Moreover, the authors report that “[w]hen duplicate reports of the same subjects were published, the publication reporting the highest talc use was selected.” The authors arbitrarily defined “frequent” as women who used talc 2 or more times per week, even though O’Brien (2020) already defined “frequent” use as greater or equal to once per week. Moreover, the authors in Woolen failed to follow their own definition, and instead cherry-picked data to include women who reported using talc 4 or more days per week. Importantly, the NCI-PDQ on Ovarian Cancer Prevention stated in regard to Woolen et al. that “because of the structure of this analysis, the results should be interpreted with care.” As mentioned above, the NCI-PDQ also concluded that the data are not adequate to support the theory of an association between ovarian cancer and perineal talcum powder exposure.¹⁴² Additionally, Woolen did not include all data from the prospective cohort studies, and seemed to selectively choose which data the authors included from these studies. For example, they included only data from women with patent reproductive tracts, ignoring the fact that women who had tubal ligation may have been exposed to talcum powder prior to their tubal ligation.

In summary, the meta-analyses rely on the accuracy of the individual studies, which would include issues related to bias and confounding.

In January 1965, Sir Austin Bradford Hill gave a presidential address to the Society of Occupational Medicine titled “The Environment and Disease: Association or Causation.”¹⁴³ He outlined 9 points, which were to be considered in determining causation with regard to exposure to various potential toxins. These included:

- Strength of Association
- Consistency
- Specificity
- Temporality
- Biological Gradient (dose-response)
- Biologic Plausibility
- Coherence

¹⁴¹ Woolen, S, et al. Association between the frequent use of perineal talcum powder products and ovarian cancer: a systematic review and meta-analysis. *J Gen Intern Med.* 2022; 37(10):2526-2532.

¹⁴² National Cancer Institute, *Ovarian, Fallopian Tube and Primary Peritoneal Cancer Prevention (PDQ): Who is at Risk?* (updated March 6, 2024) https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq#cit/section_1.11.

¹⁴³ Hill, A.B. (1965). The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine*, 58(5), 295-300.

- Experiment
- Analogy

The pertinent points for this review include strength of association, consistency, biologic gradient, biologic plausibility and experiment.

Strength of Association.

In Sir Bradford Hill's presidential address, he used two examples to demonstrate strength of association. First, the mortality of chimney sweeps was noted to be 200 times that of workers who were not exposed to chimney toxins, specifically mineral oils and tar. Second, he cited the relationship of lung cancer and smoking as referenced previously in this expert report. He noted that the death rate for smokers was nine to ten times that of non-smokers and the rate in heavy smokers was 20 to 30 times that of non-smokers. This "strength of association" discussed by Hill is lacking in the data with regard to talcum powder and ovarian cancer. Even where an association has been found, it has been weak at best. The body of data related to talcum powder and ovarian cancer extends over four decades and there is clearly no strength of association when reviewing the entire body of literature.

Consistency.

In his original presidential address, Sir Bradford Hill referenced "29 retrospective and 7 prospective inquiries (US Department of Health, Education and Welfare 1964)" that found an association between smoking and cancer.¹⁴⁴ The evidence for consistency in the published literature studying the relationship between talcum powder and ovarian cancer is particularly lacking. There are 24 case-control studies published on the topic with unique data (excluding the four case-control studies in the literature reporting on duplicative data sets). Of these 24 case-control studies, only about half showed a statistically significant association. The other half showed no association between talcum powder use and the development of ovarian cancer. The hospital-based case-control studies, which uniformly found no association, are inconsistent with the population-based case-control studies, which demonstrate inconsistent results. More importantly, none of the prospective cohort studies found an association between talcum powder use and the development of ovarian cancer, aside from the assumptions and scenarios reported by O'Brien et al in 2024. And in this article, she and her co-authors clearly state that their findings do not support causality and do not implicate any specific cancer-inducing agent. Despite Dr. Wolf's claim, "consistency" is clearly lacking in the published literature regarding talcum powder and its relationship to ovarian cancer.¹⁴⁵

Biological Gradient.

Sir Bradford Hill again used smoking and its relationship to lung cancer to demonstrate a biological gradient. He noted that the death rate due to cancer of the lung "rises linearly with the number of cigarettes smoked daily..."¹⁴⁶ This can also be termed a "dose-response relationship." There is no such

¹⁴⁴ Hill, A.B. (1965). The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine*, 58(5), 295-300.

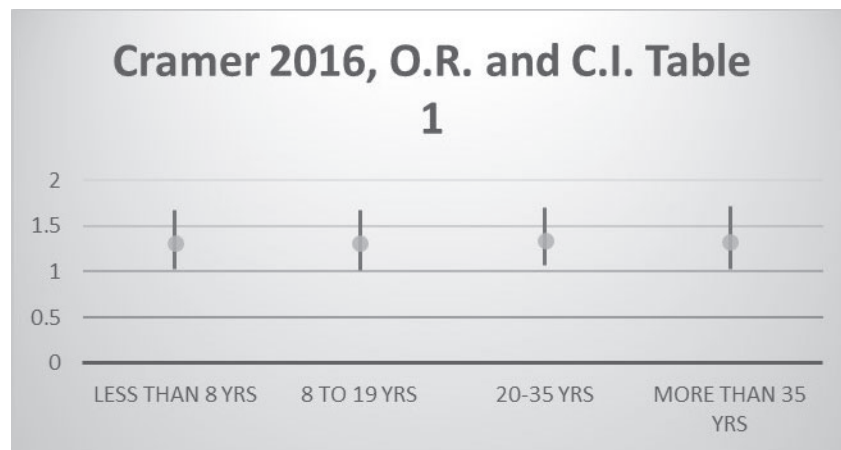
¹⁴⁵ Amended Rule 26 Expert Report of Judith Wolf, MD dated November 15, 2023, p.18.

¹⁴⁶ Hill, A.B. (1965). The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine*, 58(5), 295-300.

biologic gradient or “dose response” in the studies published on talcum powder and ovarian cancer. A couple of examples include Cramer’s 2016¹⁴⁷ study, Table 1:

Years used			
Never used	1,551 (74)	1,399 (69)	1.00 (referent)
<8	133 (6)	152 (8)	1.31 (1.03, 1.68)
8–19	126 (6)	145 (7)	1.31 (1.02, 1.68)
20–35	147 (7)	178 (9)	1.35 (1.07, 1.70)
>35	129 (6)	152 (7)	1.33 (1.03, 1.71)
P trend			0.002

The odds ratio for < 8 years is 1.31, for > 35 years the OR is very similar, 1.33.[43] Although the authors claim a trend is noted with a p-value for the trend at 0.002, if one plots the odds ratios noted above on a graph (1.31, 1.31, 1.35 and 1.33) it would be difficult to see anything other than a flat line. Likewise, the four confidence intervals on the above table are nearly exactly the same. I have plotted these data on a graph below to demonstrate the lack of a trend.



The full table 1 from Cramer 2016 is shown below.

¹⁴⁷ Cramer, D. W., Vitonis, A. F., Terry, K. L., Welch, W. R., & Titus, L. J. (2016). The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*, 27(3), 334-346.

TABLE 1. Type, Timing, and Duration of Genital Talc Use

	Control Subjects N (%)	Case Subjects N (%)	Adjusted ^a OR (95% CI)
Personal use			
None	1,099 (52)	1,001 (49)	1.00 (referent)
Body use only	452 (22)	398 (20)	0.99 (0.84, 1.16)
Genital use only	74 (4)	94 (5)	1.42 (1.04, 1.96)
Body and genital use	475 (23)	548 (27)	1.30 (1.12, 1.52)
Potential exposure in women with no personal use			
None	447 (41)	461 (46)	1.00 (referent)
Diaphragm only	207 (19)	155 (15)	0.73 (0.57, 0.93)
Condoms, with or without diaphragm	367 (33)	308 (31)	0.82 (0.66, 1.01)
Partner use, with or without diaphragm or condoms	78 (7)	77 (8)	0.96 (0.68, 1.35)
Any genital powder use			
No	1,551 (74)	1,399 (69)	1.00 (referent)
Yes	549 (26)	642 (31)	1.33 (1.16, 1.52)
Type of genital powder used			
No genital use	1,542 (73)	1,394 (68)	1.00 (referent)
Cornstarch use only	9 (<1)	5 (<1)	0.58 (0.19, 1.74)
Johnson and Johnson Baby Powder or Shower to Shower	316 (15)	363 (18)	1.30 (1.10, 1.54)
Other brand(s)	233 (11)	279 (14)	1.35 (1.12, 1.64)
Age first used genital powder ^b			
Never used	1,551 (74)	1,399 (69)	1.00 (referent)
<20	343 (16)	363 (18)	1.19 (1.01, 1.41)
20–29	122 (6)	183 (9)	1.71 (1.34, 2.17)
≥30	76 (4)	87 (4)	1.31 (0.95, 1.80)
Time since exposure ended			
No genital use	1,551 (74)	1,399 (69)	1.00 (referent)
≥35 years	51 (2)	52 (3)	1.18 (0.79, 1.75)
25–34 years	81 (4)	88 (4)	1.24 (0.91, 1.70)
15–24 years	72 (3)	82 (4)	1.30 (0.94, 1.80)
5–14 years	79 (4)	95 (5)	1.36 (1.00, 1.85)
Currently using or recently stopped	255 (12)	314 (15)	1.38 (1.15, 1.65)
<i>P</i> trend			<0.0001
Frequency of use			
No genital use	1,551 (74)	1,399 (69)	1.00 (referent)
1–7 days per month	220 (11)	227 (11)	1.17 (0.96, 1.44)
8–29 days per month	110 (5)	133 (7)	1.37 (1.05, 1.78)
≥30 days per month	205 (10)	267 (13)	1.46 (1.20, 1.78)
<i>P</i> trend			<0.0001
Years used			
Never used	1,551 (74)	1,399 (69)	1.00 (referent)
<8	133 (6)	152 (8)	1.31 (1.03, 1.68)
8–19	126 (6)	145 (7)	1.31 (1.02, 1.68)
20–35	147 (7)	178 (9)	1.35 (1.07, 1.70)
>35	129 (6)	152 (7)	1.33 (1.03, 1.71)
<i>P</i> trend			0.002
Months per year of use ^c			
No genital use	1,551 (83)	1,399 (80)	1.00 (referent)
1–3 months per year	61 (3)	60 (3)	1.11 (0.77, 1.61)
4–11 months per year	55 (3)	56 (3)	1.13 (0.77, 1.66)
12 months per year	193 (10)	229 (13)	1.35 (1.09, 1.67)
<i>P</i> trend			0.006

(Continued)

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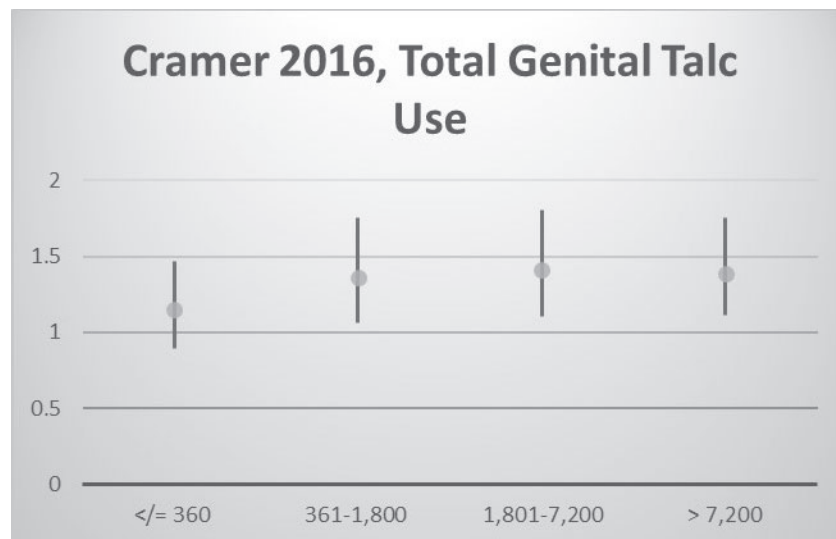
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TABLE 1. (Continued)

	Control Subjects N (%)	Case Subjects N (%)	Adjusted ^a OR (95% CI)
Total genital talc applications (apps) among only those who reported months per year of use ^c			
No genital use	1,551 (83)	1,399 (80)	1.00 (referent)
≤360 apps (equivalent to 1 year of daily use)	106 (6)	103 (6)	1.10 (0.83, 1.47)
361–1,800 apps (equivalent to >1–5 years of daily use)	79 (4)	96 (5)	1.38 (1.01, 1.88)
1,801–7,200 apps (equivalent to >5–20 years of daily use)	61 (3)	63 (4)	1.16 (0.80, 1.66)
>7,200 apps (equivalent to >20 years of daily use)	63 (3)	83 (5)	1.49 (1.06, 2.10)
<i>P</i> trend			0.02
Total genital talc applications among all (assuming 12 months/year when missing months per year of use)			
No genital use	1,551 (74)	1,399 (69)	1.00 (referent)
≤360 apps (equivalent to 1 year of daily use)	138 (7)	138 (7)	1.15 (0.89, 1.47)
361–1,800 apps (equivalent to >1–5 years of daily use)	124 (6)	148 (7)	1.36 (1.06, 1.75)
1,801–7,200 apps (equivalent to >5–20 years of daily use)	124 (6)	156 (8)	1.41 (1.10, 1.80)
>7,200 apps (equivalent to >20 years of daily use)	149 (7)	185 (9)	1.39 (1.11, 1.75)
<i>P</i> trend			0.003

^aAdjusted only for the study matching factors: reference age, study center, and study phase.^bNine cases and nine controls reported they knew that talc had been used on them in infancy so their age at exposure was recorded as 1.^cExcludes talc users from phase 1 and part of phase 2 because months/year of use was not collected.

The table above is taken from Cramer et al. 2016 and demonstrates the lack of a trend for “Total Genital Talc Use.” Cramer cites a statistically significant trend of $p < 0.003$. However, no such trend is detected when the O.R. and C.I. are represented graphically.



The below table is from Terry et al. 2013, who reported on a pooled analysis of more than 18,000 patients (8,525 cases and 9,859 controls). They also did not note a trend. Lifetime number of applications were broken down into quartiles and the odds ratios were noted to be similar among the groups. The p-value for the trend is 0.17, which is non-significant, i.e., the results are similar across the quartiles. The lack of a dose-response refutes a theory of cause and effect based on the Bradford Hill criteria.

Table 5. Association between estimated lifetime applications of genital powder and risk of ovarian cancer (borderline and invasive combined)

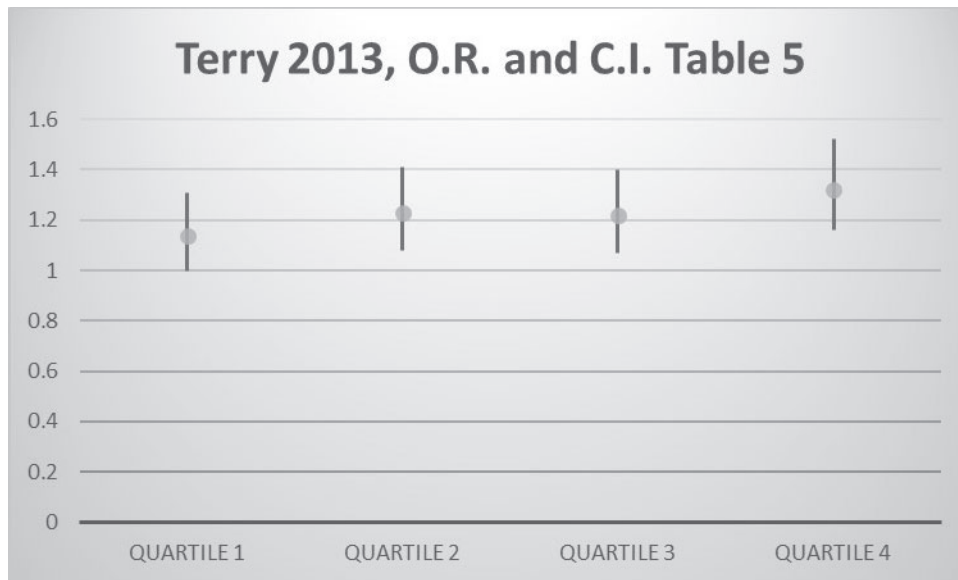
Lifetime number of applications ^a	All cases (N = 7,587)			Nonmucinous cases (N = 6,361)	
	Controls (%)	Cases (%)	OR ^b (95% CI)	Cases (%)	OR ^b (95% CI)
Never users	6,175 (76)	5,384 (71)	1.00	4,472 (70)	1.00
Quartile 1	509 (6)	534 (7)	1.14 (1.00–1.31)	467 (7)	1.18 (1.02–1.36)
Quartile 2	512 (6)	541 (7)	1.23 (1.08–1.41)	456 (7)	1.22 (1.06–1.41)
Quartile 3	497 (6)	542 (7)	1.22 (1.07–1.40)	457 (7)	1.22 (1.06–1.40)
Quartile 4	486 (6)	586 (8)	1.32 (1.16–1.52)	509 (8)	1.37 (1.19–1.58)
P _{trend} ^c			0.17		0.17

^aAge-specific 25th, 50th, and 75th percentile cutoff points are 612, 1,872, and 5,400 for participants < 40 years old; 612, 2,160, and 7,200 for 41–50 years; 720, 3,600, and 10,800 for 51–60 years; 1,440, 5,760, and 14,440 for 61–70; 840, 7,200, and 18,000 for > 70 years.

^bORs were estimated using conditional logistic regression conditioned on 5-year age groups and adjusted for age (continuous), oral contraceptive duration (never use, <2, 2–<5, 5–<10, or ≥10 years), parity (0, 1, 2, 3, or 4+ children), tubal ligation history (no or yes), BMI (quartiles), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian, or other).

^cTrend excludes never users.

When you remove the never users, and only look at the genital talc users, there is no visible dose response found as demonstrated below:



The epidemiologic literature simply does not demonstrate a biologic gradient (dose-response) with respect to the use of genital talcum powder and the development of ovarian cancer.

Biologic Plausibility

I have also evaluated whether there is a biologically plausible mechanism whereby talc could cause ovarian cancer. Plaintiff relies on several theories to try to demonstrate that genital talcum powder exposure causes ovarian cancer, but these claims are insufficient to show biologic plausibility. There is a lack of evidence that talc migrates to the pelvic cavity, and even if it did, it does not lead to chronic inflammation, let alone malignant transformation.

Migration

Plaintiff's reliance on migration of talc from the perineum to the ovaries is based on a number of studies that use a variety of materials and artificial methods in an attempt to prove that particles move upward. The female anatomy has a number of protective anatomic, functional, and physiologic measures to protect the reproductive system from contaminants. These include:

- Labia Majora are apposed from side to side, placing pressure on the Labia Minora
- Labia Minora are apposed from side to side
- Vaginal Walls are apposed anterior to posterior
- Cervical os is closed and filled with mucus
- Cervical Mucus flows downward and outward draining into the vagina
- Cervical Mucus has properties which protect the reproductive system from infection

When a woman jumps into a swimming pool, the above protective measures prevent pool water from entering the reproductive system. These protective mechanisms also prevent sand from a beach trip from traveling up the vaginal canal into the pelvis. Infertile women commonly undergo a procedure called a

Hysterosalpingogram (HSG) to determine if the fallopian tubes are patent. X-ray dye is injected into the uterus with a catheter placed through the cervix. If the system was an open system, the radiologist would simply place the contrast in the vagina and the contrast would readily flow up into the uterus and subsequently to the fallopian tubes. The cervix is most certainly closed. Plaintiff's claims of an "open system"^{148, 149} must depend on the cervix being open. As a gynecologic oncologist practicing for 30 years, when we try to gain access to the uterus, more often than not we need to use endocervical dilators in order to dilate (open) the cervix. In adult women, it is open enough to admit an endocervical cytobrush in order to obtain a Pap smear. When one does obtain a pap smear on an endocervical cytobrush, the brush is filled with thick mucus, which acts as a plug to protect the endometrium from pathogens. It is closed very tightly in nulliparous women. The vaginal canal is naturally filled with many types of bacteria and healthy yeast organisms. Yet, these bacteria and yeast do not normally move upward against the protective effects of the cervix and cervical mucus to infect the tubes and ovaries. In fact, the cervical mucus and anatomic protections of the cervix and female reproductive system are so strong that infection of the tubes and ovaries is considered pathologic and is a relatively rare event. Dr. Wolf claims that bathwater enters the vagina based on a case report publication.^{150,151} Case reports are published to inform readers of rare and unusual events in health care. It is certainly understandable that bathwater can enter the vagina on rare occasions, but it is certainly not filling the pelvis via the reproductive tract. When pathologic organisms such as *Neisseria gonorrhea* or *chlamydia trachomatis* gain access through the cervix, they do so through coitus. They then result in active infection and significant inflammation that is often painful and associated with symptoms. *E. coli* measures approximately 2 microns X 0.5 microns. *E. coli* is present on the perineum and perineal areas, but does not readily infect the fallopian tubes or ovaries. When it does, there is fever, infection and abscess formation. If the system were open, then *E.coli* should have free and unfettered access, just as talc particles are purported to have.

Published literature reporting on the possibility of upward migration of particles through the female reproductive system uses many artificial measures that do not translate into a woman applying talcum powder to her perineum. Some of these artificial conditions and measures include using oxytocin to stimulate uterine contractions, placing the woman in Trendelenburg (head tilted down, hips up), placing particulate matter in the vaginal fornix (the upper most portion of the vagina, adjacent to the cervix) as well as others. These studies do not show that powder applied to the external perineum can migrate upward into the vagina, through the cervix, uterus and fallopian tubes to the ovaries. Condoms and diaphragms have traditionally included talc as a lubricant. If any factor could confirm an association of talcum powder and ovarian cancer, it should be through the use of talc on condoms and/or diaphragms. These two methods of contraception place talcum powder immediately adjacent to the cervix, in some ways mimicking the artificial measures used by a number of migration proponents. Studies of diaphragms and condoms do not show an increased risk of ovarian cancer; in fact, Cramer 2016¹⁵² shows

¹⁴⁸ Amended Rule 26 Expert Report of Judith Wolf, MD dated November 15, 2023, p.12.

¹⁴⁹ September 14, 2021 Deposition Transcript of Judith Wolf, MD, p.581.

¹⁵⁰ Amended Rule 26 Expert Report of Judith Wolf, MD dated November 15, 2023, p.13.

¹⁵¹ September 14, 2021 Deposition Transcript of Judith Wolf, MD, p.580-581.

¹⁵² Cramer, D. W., Vitonis, A. F., Terry, K. L., Welch, W. R., & Titus, L. J. (2016). The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*, 27(3), 334-346.

a protective effect of talc-dusted diaphragms on the risk of ovarian cancer. The Cramer 1982,¹⁵³ Whittemore 1988,¹⁵⁴ Harlow 1992,¹⁵⁵ Cook 1997,¹⁵⁶ Houghton 2014,¹⁵⁷ cohort studies all show no association of condom/diaphragm use and ovarian cancer.

Literature does not demonstrate that talc can migrate upwards from the perineum

Egli 1961¹⁵⁸ used a mixture of 30% Dextran and 4% carbon black. The authors then took women who were under general anesthesia and placed them in 15° Trendelenburg (i.e., head down, hips up) and introduced a speculum in the vagina. The carbon/dextran mixture was then placed in the posterior vaginal fornix. 10 Units of Oxytocin were then given intramuscularly. Carbon was found in the tubes of two of the three women. These methods are artificial and in no way mimic the actions of a woman dusting her perineum with talcum powder.

De Boer 1972¹⁵⁹ either injected India Ink into the uterine cavity or placed it into the cervical canal of women under general anesthesia. The authors note that “Injection into the cervical canal was often difficult, with immediate flow back into the vagina.” This statement affirms my opinion that the cervix acts as a protective mechanism to prevent artificial materials from gaining access to the upper female reproductive tract. Transfer from the cervical canal occurred in almost 30% of patients, but transfer from the vagina occurred only once in 37 observations. Again, the methods of these authors do not mimic women dusting their perineum with powder.

Venter 1979¹⁶⁰ used 24 patients who had undergone general anesthesia for various conditions. They placed the patient with “buttocks slightly elevated,” using artificial measures and gravity. Like the other authors, they exposed the cervix with a speculum, confirming that the cervix cannot be visualized or seen unless the labia are spread apart artificially and the apposed vaginal walls separated. The authors then deposited 3 ml of Technetium Radioactive Colloid labeled albumin into the posterior vaginal fornix. The patients were kept in this position for 2 hours with their legs pressed together to prevent the radioactive

¹⁵³ Cramer, D. W., Welch, W. R., Scully, R. E., & Wojciechowski, C. A. (1982). Ovarian cancer and talc. A case-control study. *Cancer*, 50(2), 372-376.

¹⁵⁴ Whittemore, A. S., Wu, M. L., Paffenbarger Jr, R. S., Sarles, D. L., Kampert, J. B., Grosser, S., ... & Hendrickson, M. (1988). Personal and environmental characteristics related to epithelial ovarian cancer: II. Exposures to talcum powder, tobacco, alcohol, and coffee. *American Journal of Epidemiology*, 128(6), 1228-1240.

¹⁵⁵ Harlow, B. L., Cramer, D. W., Bell, D. A., & Welch, W. R. (1992). Perineal exposure to talc and ovarian cancer risk. *Obstetrics and Gynecology*, 80(1), 19-26.

¹⁵⁶ Cook, L. S., Kamb, M. L., & Weiss, N. S. (1997). Perineal powder exposure and the risk of ovarian cancer. *American Journal of Epidemiology*, 145(5), 459-465.

¹⁵⁷ Houghton, S. C., Reeves, K. W., Hankinson, S. E., Crawford, L., Lane, D., Wactawski-Wende, J., ... & Sturgeon, S. R. (2014). Perineal powder use and risk of ovarian cancer. *JNCI: Journal of the National Cancer Institute*, 106(9).

¹⁵⁸ Egli, G. E., & Newton, M. (1961). The transport of carbon particles in the human female reproductive tract. *Fertility and Sterility*, 12(2), 151-155.

¹⁵⁹ De Boer, C. H. (1972). Transport of particulate matter through the human female genital tract. *Reproduction*, 28(2), 295-297.

¹⁶⁰ Venter, M. (1979). Migration of particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. *South African Medical Journal*, 55(23), 917-919.

solution from streaming out of the vagina. In 3 patients, the radionuclide material streamed away from the vagina and were not counted. Of the remaining 21 cases, 16 were positive and 5 were negative for migration of the radioactive tracer to the uterus or the tube and ovaries. Again, this study used very artificial conditions, which in no way resemble a woman powdering her perineum with talc.

Sjosten 2004.¹⁶¹ All women in this study underwent examinations with gloved fingers placed into the vagina. Two control groups underwent a gynecologic exam with powder-free gloves, and two groups underwent a gynecologic exam with powdered gloves. There were significantly more starch particles, as well as large particles, found in the uterus and cervix after examination with powdered gloves. These artificial conditions do not mimic a woman powdering her perineum with talcum powder.

Wehner 1986¹⁶² studied their artificial methods in monkeys. The monkeys were sedated with 25 mg of ketamine hydrochloride. Each of the monkeys was then restrained by taping their hands and tails to a plywood restraining cross. The pelvis was elevated to 25-30 degrees (head down, pelvis up) and the legs were held with the knees bent close to the chest using a Velcro strap as a restraining mechanism. Each of the monkeys was then injected with an artificially produced talc slurry placed into the vaginal fornix. Once a week, the monkeys were injected with 10 units of oxytocin to stimulate uterine contractions. This was repeated 30 times in each monkey. Two days after the 30th injection of talc into the posterior vaginal fornix, peritoneal lavage was carried out. The authors concluded that no measurable quantities of talc, deposited by multiple applications in the vaginal fornix of the cynomolgus monkey, translocated to the uterus or beyond.

Pathology Studies

Published literature reporting on pathology has not shown a correlation between talcum powder use and findings of talc particles in tissue. The studies fail to find foreign body reaction, which is an expected response in human tissue when exposed to foreign material like talcum powder, and cannot rule out contamination from the acquisition and physical manipulation by the pathology department.

Heller 1996¹⁶³ studied 24 women who were undergoing gynecologic surgery. They separated the women into two groups, those exposed to talc and those unexposed to talc. The authors then looked at the ovaries microscopically. These authors found that 12/12 women with known talc exposure had talc in the ovaries, while 11/12 of the women with no talc exposure (unexposed) also had talc found in the ovaries. Notably, the authors state that “the quantity detected in this study did not correlate well with the reported exposure.” This raises the question: Did the talc come from laboratory contamination or other contamination of specimens? H&E evaluation of tissue from one subject failed to reveal the expected tissue reaction to talc, further supporting contamination as a potential explanation for the findings.

¹⁶¹ Sjosten, A. C. E., Ellis, H., & Edeltam, G. A. B. (2004). Retrograde migration of glove powder in the human female genital tract. *Human Reproduction*, 19(4), 991-995.

¹⁶² Wehner, A. P., Weller, R. E., & Lepel E. A. (1986). On talc translocation from the vagina to the oviducts and beyond. *Food and Chemical Toxicology*, 24, 329-38.

¹⁶³ Heller, D. S., Westhoff, C., Gordon, R. E., & Katz, N. (1996). The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *American Journal of Obstetrics and Gynecology*, 174(5), 1507-1510.

Cramer 2007¹⁶⁴ reported on a case of a 68-year-old woman who reported using talc daily for 30 years. The authors examined pelvic lymph nodes obtained from the patient's ovarian cancer surgery for evidence of talc particles. The authors note that no distinct particulates were seen under regular light microscopy. They did find evidence of birefringence using polarizing microscopy, and 3 of the 4 nodes (all 4 without ovarian cancer) were found to have polarizing material. Nothing is mentioned in the publication regarding contamination of the specimen from powders, particulates or contaminants from handling the specimen, either in the operating room or in the lab. This is a case report, the lowest form of evidence, and there were no controls for comparison.

McDonald 2019¹⁶⁵ reported on 22 women who had undergone surgery at the Brigham and Women's Hospital between 2004 and 2005. Cases were eligible if they had lymph nodes removed. The authors performed what they referred to as a "semi-quantitative visual estimate of surface contamination," confirming that contamination from various sources is a valid and real factor in these pathology studies. They point out that specimens may be contaminated during the acquisition and by physical manipulation as well as handling steps in the Pathology Department. I have personally visited dozens of pathology departments at various hospitals throughout the Southeast and can confirm that there are myriad opportunities for contamination of specimens with dust, talc, fibers or other contaminants.

McDonald 2019¹⁶⁶ published another article about 6 months after the manuscript referenced above. Typically, a foreign body reaction to talc would be seen under the microscope, including multinucleated giant cells and granulomas sequestering the talc particles. The authors found talc particles widely present throughout the specimens that they analyzed in the 5 cases reported on in this manuscript. However, according to the authors, multinucleate giant cells coalescing as part of an inflammatory response were only seen in rare instances.

STIC Lesions

Serous Tubal Intraepithelial Carcinoma (STIC) lesions are the precursor or non-invasive form of HGSC. STIC lesions are seen more commonly in surgical specimens taken from women undergoing a prophylactic, risk-reducing bilateral salpingectomy in order to lower their risk of ovarian cancer. Many of these women have a family history of ovarian cancer and/or breast cancer and/or a BRCA1/BRCA2 mutation or other genetic mutation that put them at increased risk of ovarian cancer. Inflammation is not associated with STIC lesions; nor is evidence of inflammation seen either grossly or microscopically in these women. Malmberg et al. reported on this in 2016 and found no evidence of inflammation or inflammatory markers

¹⁶⁴ Cramer, D. W., Welch, W. R., Berkowitz, R. S., & Godleski, J. J. (2007). Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. *Obstetrics & Gynecology*, 110(2), 498-501.

¹⁶⁵ McDonald, S. A., Fan, Y., Welch, W. R., Cramer, D. W., Stearns, R. C., Sheedy, L., ... & Godleski, J. J. (2019). Correlative polarizing light and scanning electron microscopy for the assessment of talc in pelvic region lymph nodes. *Ultrastructural Pathology*, 43(1), 13-27.

¹⁶⁶ McDonald, S. A., Fan, Y., Welch, W. R., Cramer, D. W., & Godleski, J. J. (2019). Migration of talc from the perineum to multiple pelvic organ sites: five case studies with correlative light and scanning electron microscopy. *American Journal of Clinical Pathology*, 152(5), 590-607.

associated with STIC lesions.¹⁶⁷ Grossly, inflammation of the fallopian tube and/or ovary would result in erythema, induration, adhesions, and in advanced cases, purulence. None of these features are commonly seen when operating on women undergoing a prophylactic bilateral salpingectomy.

Inflammation

The medical and scientific literature does not support inflammation as a mechanism for ovarian cancer development. Inflammation and inflammatory markers are associated with advanced ovarian cancer. Trabert in 2014 studied 46 biomarkers of inflammation in specimens from the PLCO trial.¹⁶⁸ Specimens of 149 patients from the PLCO trial were analyzed and compared to 149 matched controls. They found that elevated markers of inflammation were associated with ovarian cancer risk. The PLCO trial, however, was a screening trial for ovarian cancer that failed to diagnose the cancers early. In fact, the vast majority of ovarian cancer patients in the PLCO trial were diagnosed at advanced stages of ovarian cancer. As a result, while the specimens were in fact “pre-diagnostic,” they were pre-diagnostic of advanced ovarian cancer in the majority of cases. Therefore, what Trabert actually found was that advanced ovarian cancer may be associated with an elevation of a few non-specific inflammatory markers when compared to controls. Many authors use CRP (C-Reactive Protein), Interleukin 1alpha and/or Tumor Necrosis Factor (TNF) as markers of general systemic inflammation. These serum markers of inflammatory response are extremely non-specific and may be elevated in any inflammatory condition.^{169,170} This error has been repeated by dozens of well-meaning researchers and scientists. In order to prove that chronic inflammation is a cause of ovarian cancer, one must find these elevated markers in women who do not yet have ovarian cancer, and then follow them until cancer is detected.

Contrary to Trabert, Huang et al. examined the relationship between lifetime ovulatory years and inflammation in women. Their findings did not support elevated systemic inflammation as the underlying mechanism linking higher lifetime ovulatory years with increased ovarian risk. Huang, et al. studied the estimated number of lifetime ovulatory cycles in samples from the Women’s Health Study, as well as the Women’s Health Study II.¹⁷¹ They concluded that an increased number of lifetime ovulatory cycles was actually associated with a decrease in circulating inflammatory markers such as C-reactive protein (CRP).

¹⁶⁷ Malmberg, K., Klynning, C., Flöter-Rådestad, A., & Carlson, J. W. (2016). Serous tubal intraepithelial carcinoma, chronic fallopian tube injury, and serous carcinoma development. *Virchows Archiv*, 468(6), 707-713.

¹⁶⁸ Trabert, B., Pinto, L., Hartge, P., Kemp, T., Black, A., Sherman, M. E., ... & Wentzensen, N. (2014). Pre-diagnostic serum levels of inflammation markers and risk of ovarian cancer in the prostate, lung, colorectal and ovarian cancer (PLCO) screening trial. *Gynecologic Oncology*, 135(2), 297-304.

¹⁶⁹ Trabert, B., Pinto, L., Hartge, P., Kemp, T., Black, A., Sherman, M. E., ... & Wentzensen, N. (2014). Pre-diagnostic serum levels of inflammation markers and risk of ovarian cancer in the prostate, lung, colorectal and ovarian cancer (PLCO) screening trial. *Gynecologic Oncology*, 135(2), 297-304.

¹⁷⁰ McSorley, M. A., Alberg, A. J., Allen, D. S., Allen, N. E., Brinton, L. A., Dorgan, J. F., ... & Helzlsouer, K. J. (2007). C-reactive protein concentrations and subsequent ovarian cancer risk. *Obstetrics & Gynecology*, 109(4), 933-941.

¹⁷¹ Huang, T., Shafrir, A. L., Eliassen, A. H., Rexrode, K. M., & Tworoger, S. S. (2020). Estimated number of lifetime ovulatory years and its determinants in relation to levels of circulating inflammatory biomarkers. *American Journal of Epidemiology*, 189(7), 660-670.

Inflammation and inflammatory markers are associated with advanced ovarian cancer. There is no evidence, however, that inflammation and inflammatory markers are associated with the development or progression of STIC lesions, the earliest form of HGSC. There is no evidence that inflammation leads to ovarian cancer or causes ovarian cancer. There is a huge volume of data supporting the association of inflammation with advanced ovarian cancer as well as with ovarian cancer cell lines, which are grown from cells of patients with advanced ovarian cancer. Inflammation, however, does not cause ovarian cancer.

Cornstarch

Dr. Wolf states in her expert report that cornstarch is a safer alternative to talc for use on surgical gloves, and that “starch, unlike talc, is not an irritant.”¹⁷² The FDA, however, banned the use of powder (both talc and cornstarch) on surgical gloves, a decision that had nothing to do with the risk of cancer, but was instead based on the fact that powders (both talc and cornstarch) are capable of causing adhesions. Several publications have likewise reported on the potential hazards of using cornstarch on medical gloves.^{173, 174} Moreover, when applied to the perineum in a hot, humid environment, cornstarch may also increase the risk of yeast infections.

NSAIDs and PID

There are also no clear and consistent data that anti-inflammatory agents such as aspirin, acetaminophen, ibuprofen and other non-steroidal anti-inflammatory drugs (NSAIDs) consistently reduce the risk of the development of ovarian cancer. One example of the inconsistency of studies looking at aspirin and NSAIDs and their risk-reducing properties is the Nurses’ Health Study analysis by Barnard, et al.¹⁷⁵ The authors found a risk reduction with regular users of low-dose aspirin, yet an increased risk with long-term, chronic use of NSAIDs. NSAIDs are known to reduce inflammation and are widely used for chronic inflammatory conditions such as a sore knee, a sore hip, back pain, etc. If inflammation were a cause of ovarian cancer, then NSAIDs should reduce the risk. Additionally, in the United States, national organizations, with the exception of ACS, that have released statements regarding risk factors for ovarian cancer do not recommend taking aspirin or NSAIDs to reduce one’s risk of ovarian cancer. The ACS states that “[a]ccumulating evidence suggests that frequent aspirin use is also associated with reduced risk, although this can have serious adverse health effects.”¹⁷⁶ However, this is not congruent with recommendations of other national societies and organizations. The only agent recommended by SGO and ACOG to reduce one’s risk of ovarian cancer is oral contraceptive pills (OCPs). OCPs are effective at reducing the risk of the development of ovarian cancer by up to 50% when taken for 5 years or more. This risk reduction is seen even in women with the BRCA1/BRCA2 genetic mutation.

¹⁷² Amended Rule 26 Expert Report of Judith Wolf, MD dated November 15, 2023, p.16.

¹⁷³ Ruhl C. et al. A new hazard of cornstarch, an absorbable dusting powder. 1994. *Journal of Emergency Medicine*, 12(1), 11-14.

¹⁷⁴ Edlich R. et al. Dangers of cornstarch powder on medical gloves. 2009. *Annals of Plastic Surgery*, 63(1), 822-826.

¹⁷⁵ Barnard, M. E., Poole, E. M., Curhan, G. C., Eliassen, A. H., Rosner, B. A., Terry, K. L., & Tworoger, S. S. (2018). Association of analgesic use with risk of ovarian cancer in the Nurses’ Health Studies. *JAMA oncology*, 4(12), 1675-1682.

¹⁷⁶ American Cancer Society. (2024). Cancer Facts & Figures 2024. *American Cancer Society*.

Pelvic inflammatory disease (PID) is an infection of the fallopian tubes and ovaries and results in scarring and infertility because of inflammation. It is commonly caused by sexually transmitted disease (STD) through coitus. Common organisms causing PID include *Neisseria Gonorrhea* and *Chlamydia Trachomatis* and subsequently a multi-organism anaerobic infection generally ensues. Clinically, patients presenting with PID have significant signs of pelvic inflammation noted on physical exam. Such signs include exquisite pelvic tenderness, cervical motion tenderness commonly described as a “chandelier sign,” lower abdominal and pelvic tenderness, and in some cases an acute abdomen with guarding and rebound. These infections are generally treated with hospitalization, intravenous antibiotics and surgical or radiologic drainage of any abscess. With all of this severe inflammation of the fallopian tubes and ovaries, we do not see a consistent increase in the risk of ovarian cancer over time. Ovarian cancer as a risk or sequelae of PID is not mentioned by our national organizations such as ACOG, SGO, and NCI, nor is it routinely a part of patient counselling.

Merritt et al. 2008¹⁷⁷ studied 1,576 cancer patients and compared them to 1,509 controls in the Australian Cancer Study and the Australian Ovarian Cancer Study Group. They found no reduction in risk of ovarian cancer with the use of aspirin or NSAIDs, as noted in the table below:

TABLE IV – ASSOCIATION BETWEEN ANTI-INFLAMMATORY MEDICATION USE IN THE PAST 5 YEARS AND RISK OF EPITHELIAL OVARIAN CANCER							
	Controls ¹ N (%)	All cases ¹ N (%)	All cases (N = 1,576) OR ² (95% CI)	Serous (N = 994) OR ² (95% CI)	Mucinous (N = 191) OR ² (95% CI)	Endometrioid (N = 141) OR ² (95% CI)	Clear cell (N = 88) OR ² (95% CI)
Aspirin							
Never	772 (51)	783 (50)	1.0	1.0	1.0	1.0	1.0
Ever	730 (49)	781 (49)	1.06 (0.92–1.23)	1.06 (0.90–1.25)	0.99 (0.72–1.35)	0.92 (0.64–1.32)	0.92 (0.58–1.45)
≤1/week	612 (41)	650 (41)	1.06 (0.91–1.23)	1.05 (0.88–1.25)	0.98 (0.71–1.36)	0.98 (0.68–1.43)	0.95 (0.59–1.54)
≥2/week	118 (8)	131 (8)	1.06 (0.80–1.41)	1.11 (0.81–1.51)	1.02 (0.52–2.03)	0.56 (0.23–1.34)	0.75 (0.30–1.89)
p-Value (trend)			0.5	0.4	0.99	0.4	0.6
NSAIDs							
Never	625 (42)	723 (46)	1.0	1.0	1.0	1.0	1.0
Ever	878 (58)	836 (54)	0.88 (0.76–1.02)	0.93 (0.78–1.10)	0.69 (0.50–0.94)	0.76 (0.53–1.09)	0.92 (0.58–1.45)
≤1/week	653 (43)	625 (40)	0.90 (0.76–1.05)	0.94 (0.78–1.12)	0.73 (0.53–1.02)	0.73 (0.50–1.09)	0.97 (0.59–1.60)
≥2/week	225 (15)	211 (14)	0.83 (0.66–1.04)	0.90 (0.70–1.16)	0.51 (0.28–0.93)	0.84 (0.49–1.44)	0.79 (0.39–1.58)
p-Value (trend)			0.1	0.3	0.01	0.3	0.6

¹Numbers may not sum to total because of missing data.–²Adjusted for age, education, parity and oral contraceptive pill use.

¹Numbers may not sum to total because of missing data. ²Adjusted for age, education, parity and oral contraceptive pill use.

Additionally, there was no association between PID and ovarian cancer, as noted in the table below from the same publication:

¹⁷⁷ Merritt, M. A., Green, A. C., Nagle, C. M., Webb, P. M., & Australian Cancer Study (Ovarian Cancer) and Australian Ovarian Cancer Study Group. (2008). Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *International Journal of Cancer*, 122(1), 170-176.

TABLE III – ASSOCIATION BETWEEN SELF-REPORTED MEDICAL CONDITIONS POTENTIALLY ASSOCIATED WITH INFLAMMATION OF THE OVARIES AND RISK OF EPITHELIAL OVARIAN CANCER

	Controls ¹ N (%)	All cases ¹ N (%)	All cases (N = 1,576) OR ² (95% CI)	Serous (N = 994) OR ² (95% CI)	Mucinous (N = 191) OR ² (95% CI)	Endometrioid (N = 141) OR ² (95% CI)	Clear cell (N = 88) OR ² (95% CI)
PID							
Never	1,406 (94)	1,460 (93)	1.0	1.0	1.0	1.0	1.0
Ever	84 (6)	103 (7)	1.15 (0.85–1.57)	0.96 (0.66–1.38)	1.46 (0.82–2.60)	1.29 (0.66–2.52)	0.87 (0.30–2.49)
Genital herpes							
Never	1,420 (98)	1,425 (97)	1.0	1.0	1.0	1.0	1.0
Ever	35 (2)	42 (3)	1.17 (0.73–1.87)	1.65 (1.01–2.69)	0.40 (0.09–1.71)	0.32 (0.04–2.37)	0.74 (0.10–5.63)
HPV infection							
Never	1,148 (78)	1,197 (81)	1.0	1.0	1.0	1.0	1.0
Ever	317 (22)	273 (19)	0.94 (0.78–1.15)	0.92 (0.74–1.15)	0.98 (0.66–1.45)	1.58 (1.03–2.44)	0.72 (0.36–1.47)
Mumps							
Never	496 (76)	508 (75)	1.0	1.0	1.0	1.0	1.0
Ever (postpubertal)	160 (24)	164 (25)	0.96 (0.73–1.25)	1.06 (0.79–1.42)	0.78 (0.40–1.49)	0.97 (0.50–1.87)	0.81 (0.35–1.92)
Endometriosis ³							
Never	1,413 (94)	1,431 (92)	1.0	1.0	1.0	1.0	1.0
Ever	87 (6)	124 (8)	1.31 (0.97–1.78)	1.14 (0.80–1.62)	0.89 (0.46–1.75)	1.85 (1.02–3.38)	2.66 (1.31–5.44)
Long periods ³ (> 7 days)							
Never/rarely	1,174 (82)	1,173 (82)	1.0	1.0	1.0	1.0	1.0
Often	188 (13)	192 (14)	1.05 (0.83–1.31)	1.05 (0.81–1.36)	0.70 (0.40–1.22)	1.23 (0.71–2.12)	1.26 (0.62–2.53)
Always	75 (5)	62 (4)	0.79 (0.55–1.13)	0.82 (0.55–1.23)	0.78 (0.34–1.78)	0.72 (0.27–1.85)	0.83 (0.24–2.83)
Painful periods ³							
Never/rarely	760 (52)	711 (49)	1.0	1.0	1.0	1.0	1.0
Sometimes	290 (20)	301 (20)	1.04 (0.85–1.27)	1.04 (0.83–1.31)	0.95 (0.61–1.47)	1.07 (0.65–1.75)	1.13 (0.59–2.15)
Often	404 (28)	452 (31)	1.17 (0.98–1.40)	1.17 (0.96–1.43)	1.12 (0.77–1.64)	1.12 (0.72–1.73)	1.14 (0.65–2.00)

¹Numbers may not sum to total because of missing data. ²Adjusted for age, education, parity and oral contraceptive pill use. ³Additionally adjusted for body mass index one year prior to diagnosis.

Wu et al. 2009¹⁷⁸ studied 609 cases in Los Angeles County and compared them to 688 population-based controls in an effort to study the relationship between inflammation and ovarian cancer. They found no evidence of a protective effect for the use of NSAIDs. They actually found an increased risk of ovarian cancer with increasing frequency of use of NSAIDs consistent across all types of NSAIDs, as shown in the table below. This increasing risk was associated with aspirin, acetaminophen, and other NSAIDs as well. If inflammation were a cause of ovarian cancer, then one would expect that taking anti-inflammatory agents would negate this risk. We simply do not see this demonstrated consistently in the medical literature.

¹⁷⁸ Wu, A. H., Pearce, C. L., Tseng, C. C., Templeman, C., & Pike, M. C. (2009). Markers of inflammation and risk of ovarian cancer in Los Angeles County. *International Journal of Cancer*, 124(6), 1409-1415.

TABLE IV – MULTIVARIABLE RRS¹ (95% CIs) FOR USE OF ALL NSAIDs (ASPIRIN, ACETAMINOPHEN, OTHER NSAIDs) AND RISK OF OVARIAN CANCER

	Excluded medication use the 2 years before reference date		
	Cases	Controls	RR (95% CI)
All NSAIDs			
Years of use			
Never ²	355	486	1.00
1 to 5 yr	117	99	1.71 (1.23–2.39)
>5 to ≤10 yr	37	33	1.59 (0.93–2.72)
>10 yr	79	57	1.81 (1.21–2.71)
p trend			<0.001
No. of pills per week			
Never ²	355	486	1.00
1 to ≤7/wk	82	66	1.62 (1.11–2.39)
>7 to ≤14/wk	41	49	1.09 (0.67–1.78)
>14/wk	110	74	2.24 (1.56–3.21)
p trend			<0.001
Total no. of pills			
Never	355	486	1.00
1 to ≤1096	73	63	1.60 (1.08–2.38)
>1096 to 6428	73	66	1.43 (0.96–2.13)
>6428	87	60	2.22 (1.49–3.31)
p trend			<0.001
Years of use by type ³			
Aspirin			
Never ²	492	597	1.00
1 to 5 yr	46	25	2.13 (1.21–3.77)
>5 to ≤10 yr	13	18	0.70 (0.31–1.58)
>10 yr	31	28	1.15 (0.62–2.13)
p trend			0.43
Acetaminophen			
Never ²	491	590	1.00
1 to 5 yr	47	53	0.87 (0.53–1.41)
>5 yr	44	25	1.71 (0.94–3.09)
p trend			0.12
Other NSAIDs			
Never ²	450	575	1.00
1 to 5 yr	87	61	1.76 (1.18–2.63)
>5 to ≤10 yr	17	19	1.18 (0.55–2.53)
>10 yr	28	13	2.18 (1.03–4.63)
p trend			0.008
Frequency of use by type ³			
Aspirin			
Never ²	492	597	1.00
1 to ≤7/wk	61	48	1.49 (0.94–2.35)
>7	29	23	1.18 (0.61–2.29)
p trend			0.21
Acetaminophen			
Never ²	491	590	1.00
1 to ≤7/wk	48	45	1.04 (0.63–1.71)
>7 /wk	43	33	1.36 (0.78–2.36)
p trend			0.33
Other NSAIDs			
Never ²	450	575	1.00
1 to ≤7/wk	52	38	1.56 (0.95–2.56)
>7 to ≤14/wk	29	25	1.27 (0.68–2.40)
>14/wk	51	30	2.22 (1.30–3.79)
p trend			0.0009

Wu et al. also found no association between a history of PID and ovarian cancer with an O.R. 1.48, C.I. 0.78–2.82.

IUD

IUDs are associated with inflammation, which is part of their mechanism of action, but have a protective effect against ovarian cancer. Wheeler et al. 2019¹⁷⁹ published a systematic review and meta-analysis of data regarding IUDs and ovarian cancer. They found 15 studies that met their criteria and found that IUDs actually have a protective effect. The association between IUD use and ovarian cancer was found to be O.R. 0.68, C.I. 0.62-0.75, a 32% decreased risk. These authors note that “[a]ll IUD’s, whether steel, copper, or hormone-releasing, elicit a localized inflammatory response from the presence of a foreign body which keeps immune cells active locally, potentially eradicating occult microscopic cancer cells.”¹⁸⁰

Talc-Related Inflammation Does Not Cause Cancer

Pleurodesis

Talcum powder is commonly used for pleurodesis in patients with chronic pleural effusions. While Ghio et al. 2001¹⁸¹ concluded that talc should not be used for pleurodesis in patients with non-malignant pleural effusions, other authors have come to the opposite conclusion. Korsic et al. 2015¹⁸² studied 107 patients with malignant pleural effusion; 56/107 were managed with pleurodesis using talc and the remaining 51/107 were managed with serial thoracentesis. The group managed with talc pleurodesis actually had a significantly longer survival of 21.5 weeks, compared to only 9 weeks in the serial thoracentesis group ($p<0.001$). Another paper, Nasreen et al. 2000,¹⁸³ noted that talc pleurodesis is an accepted method of pleurodesis, and in fact is an FDA-approved use of talcum powder for pleurodesis. The authors studied apoptosis (death of malignant cells) in malignant mesothelioma cells and compared it to normal pleural mesothelial cells grown in cell culture when exposed to talc. They found that talc induces apoptosis (cell death) in the malignant mesothelioma cells but not in normal pleural mesothelial cells ($p<0.05$). Lee et al., in their letter to the editor in February 2010, also noted that talc causes selective apoptosis (cell death) of lung cancer cells and spares normal mesothelial cells.¹⁸⁴ Hunt et al. reported that pleurodesis is safe for young patients who experience primary spontaneous pneumothorax. The authors studied papers

¹⁷⁹ Wheeler, L. J., Desanto, K., Teal, S. B., Sheeder, J., & Guntupalli, S. R. (2019). Intrauterine device use and ovarian cancer risk: a systematic review and meta-analysis. *Obstetrics & Gynecology*, 134(4), 791-800.

¹⁸⁰ Wheeler, L. J., Desanto, K., Teal, S. B., Sheeder, J., & Guntupalli, S. R. (2019). Intrauterine device use and ovarian cancer risk: a systematic review and meta-analysis. *Obstetrics & Gynecology*, 134(4), 791-800.

¹⁸¹ Ghio, A. J., Roggli, V., & Light, R. W. (2001). Talc should not be used for pleurodesis in patients with nonmalignant pleural effusions. *American Journal of Respiratory and Critical Care Medicine*, 164(9), 1741.

¹⁸² Korsic, M., Badovinac, S., Cucevic, B., & Janevski, Z. (2015). Talc pleurodesis improves survival of patients with malignant pleural effusions: case-control study. *Wiener Klinische Wochenschrift*, 127(23-24), 963-969.

¹⁸³ Nasreen, N., Mohammed, K. A., Dowling, P. A., Ward, M. J., Galffy, G., & Antony, V. B. (2000). Talc induces apoptosis in human malignant mesothelioma cells in vitro. *American Journal of Respiratory and Critical Care Medicine*, 161(2), 595-600.

¹⁸⁴ Lee P., et al. Selective apoptosis of lung cancer cells with talc. *European Respiratory Journal*. 2010; 3:450-452.

reporting patients with talc pleurodesis and with long-term follow-up, and no cancers developed.¹⁸⁵ Talcum powder is the preferred, FDA-approved agent for pleurodesis, and I have recommended it to my patients over my 30+ year career, and continue to recommend it to my patients.

EXPERIMENT

There are no experiments, in animals or humans, demonstrating that talcum powder causes ovarian cancer. Specifically, there are no animal studies in which talcum powder is administered to animals and the animals subsequently develop ovarian cancer.

Malignant Transformation

There are no studies showing that sprinkling talcum powder on benign ovarian cells in cell culture causes them to transform into malignant cells. Nor are there any studies that demonstrate a step-wise progression from benign ovarian cells exposed to talc to malignant cells in the process of malignant transformation. I will briefly review a few publications which Plaintiff wrongly claims support malignant transformation.

Shukla et al. 2009¹⁸⁶ reported alterations in gene expression with regard to mesothelial cells and mineral pathogenicity. Their group exposed human mesothelial cells, as well as human ovarian epithelial cells, to asbestos, talc and titanium dioxide for various lengths of time. The ovarian surface epithelial cells were from an SV40 Tag immortalized cell line titled “IOSE 398.” After exposure to these various elements, they studied changes in gene expression. In their final analysis, they did not see malignant transformation of these ovarian cells. Their objective “was to compare acute toxicity and gene expression profiles of crocidolite asbestos....” While the authors note that IOSE cells are not implicated in asbestos-induced diseases, they were included for comparison, as they have occasionally been linked to talc use and ovarian cancer, “although such links are highly controversial.”

In the present case of talc causing malignant transformation, the appropriate endpoint would be transforming benign ovarian cells into malignant ovarian cancer cells. This has simply never been done. One example of an inappropriate surrogate are the genetic changes reported by Shukla et al.¹⁸⁷

Likewise, **Buz’Zard et al. 2007**¹⁸⁸ reported on the use of “Pycnogenol,” which is a proprietary mixture of water-soluble flavonoids extracted from a French Pine Tree to induce what they referred to as “Talc-

¹⁸⁵ Hunt I., et al. Is talc pleurodesis safe for young patients following primary spontaneous pneumothorax? *Interactive Cardiovascular and Thoracic Surgery*. 2007; 6(1):117-20.

¹⁸⁶ Shukla, A., MacPherson, M. B., Hillegass, J., Ramos-Nino, M. E., Alexeeva, V., Vacek, P. M., ... & Mossman, B. T. (2009). Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity. *American Journal of Respiratory Cell and Molecular Biology*, 41(1), 114-123.

¹⁸⁷ Shukla, A., MacPherson, M. B., Hillegass, J., Ramos-Nino, M. E., Alexeeva, V., Vacek, P. M., ... & Mossman, B. T. (2009). Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity. *American Journal of Respiratory Cell and Molecular Biology*, 41(1), 114-123.

¹⁸⁸ Buz’Zard, A. R., & Lau, B. H. (2007). Pycnogenol® reduces talc-induced neoplastic transformation in human ovarian cell cultures. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, 21(6), 579-586.

induced Neoplastic Transformation in Ovarian Cell Cultures.” In this study, the authors did not induce malignant transformation of normal ovarian cells. The “malignant” cell line that they chose was a line of Ovarian Granulosa Cells. Granulosa Cell Tumors are rare ovarian tumors that are very different from Epithelial Ovarian Cancers. Granulosa Cell Tumors are generally very slow-growing and not very aggressive. They are generally not treated with chemotherapy as they are not chemo-sensitive. These authors measured the ability of cells to grow suspended in “soft agar”; they also measured ROS generation and “cell viability.” Immortal cells typically grow in soft agar. They never demonstrated dose-response or the ability of talc to convert benign ovarian cells into malignant cells (“malignant transformation”), but instead claim to have demonstrated several surrogate measures. Surrogates have been proven to be inaccurate measures of the ultimate endpoint which is sought to be proven.¹⁸⁹ The authors state in the first paragraph of their discussion: “Cancer development is a multi-step process comprising a series of cellular and molecular changes that are mediated by various endogenous and exogenous stimuli, such as aberrantly expressed ROS...A characteristic of neoplastically transformed cells is their ability to grow and to divide when held in suspension...”¹⁹⁰ They describe the activity and characteristics of these benign cells but are never able to demonstrate transformation into a malignant cell line.

Emi et al. reported on epigenomic and transcriptomic changes in a macrophage model when exposed to talc and estrogen.¹⁹¹ This study only looked at macrophages, and not ovarian or fallopian tube cell lines. The macrophage cell line showed changes in a “gene chip microarray profile,” which is not equivalent to malignant transformation. Moreover, this study only shows an acute inflammatory reaction based on one 24-hour application, and thus is irrelevant to a woman applying talc to her perineum.

Dr. Wolf also cites to an in vitro study by **Harper et al.** for the supposed finding of neoplastic transformation when cells in culture were exposed to talcum powder.¹⁹² The authors in this study only reviewed a “cell transformation assay” as well as “colony formation.”¹⁹³ Additionally, ovarian cell lines purchased and grown in a lab do not represent or mimic the cells from the distal fallopian tube. If a single application of talcum powder actually did cause malignant transformation in these commercially purchased cell lines, and if talcum powder is so commonly used, why is ovarian cancer a rare disease? Dr. Ghassan Saed was a co-author of this paper and disclosed that he is a paid consultant and expert witness for the plaintiffs in the talcum powder litigation, which injects potential bias. It is also worth noting that before finally being accepted by *Minerva Obstetrics and Gynecology*, the manuscript was rejected by 5

¹⁸⁹ Yudkin, J. S., Lipska, K. J., & Montori, V. M. (2011). The idolatry of the surrogate. *British Medical Journal*, 343.

¹⁹⁰ Buz'Zard, A. R., & Lau, B. H. (2007). Pycnogenol® reduces talc-induced neoplastic transformation in human ovarian cell cultures. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, 21(6), 579-586.

¹⁹¹ Emi T et al. Transcriptomic and epigenomic effects of insoluble particles on J774 macrophages. 2021. *Epigenetics*, 16(10), 1053-1070.

¹⁹² Amended Rule 26 Expert Report of Judith Wolf, MD dated November 15, 2023, p.15.

¹⁹³ Harper AK, et al. Talcum powder induces malignant transformation in normal human primary ovarian epithelial cells. *Minerva Obstetrics and Gynecol.* 2023 Apr;75(2):150-157.

other peer-reviewed journals. One reviewer described the authors' conclusions as "outrageous and not supported by the manuscript's data."¹⁹⁴

Dr. Saed's earlier cell studies also fail to show malignant transformation.^{195,196, 197} In the 2019 publication, the authors' objective was to "determine the effects of talcum powder on the expression of key redox enzymes, CA-125 levels, and cell proliferation and apoptosis in normal and EOC cells."¹⁹⁸ This study, however, only contains findings regarding surrogates, not the true endpoint that they seek. The authors claim to have demonstrated increased CA-125 levels, as well as inhibition of apoptosis, alteration of key redox and inflammatory markers and enhancement of cell proliferation. None of these constitutes malignant transformation. Using surrogates such as these to claim a cause and effect of talc on malignant transformation is simply not accurate. CA-125 levels may be elevated in benign conditions such as endometriosis, uterine fibroids, cholecystitis and many other benign conditions. It can also be elevated during a normal menstrual period. Additionally, CA-125 has not been shown to be related to any causative agent related to ovarian cancer. Similarly, the two Saed posters use various endpoints looking at cells grown in a lab to demonstrate what they call malignant transformation. Properties such as "growth into soft agar" or the "Abcam assay" are other surrogates.¹⁹⁹ These are not evidence of malignant transformation. In short, the series of studies by Dr. Saed contain dubious practices and results, and do not demonstrate malignant transformation of benign ovarian cells.

Conclusion

In short, there is no biologically plausible mechanism by which genital talcum powder use causes ovarian cancer. Even if one were to concede that talc particles applied to the perineum find their way from the external perineum into the vagina, upward against gravity and against the many physical, anatomic and physiologic protective barriers of the female reproductive system, they are not causing ovarian cancer. There is no evidence to support the existence of talc-related inflammation in the female reproductive tract and no evidence that talc-related inflammation has the ability to cause cancerous changes in cells of

¹⁹⁴ SAED_SEPT222021_SUPPL_000101.

¹⁹⁵ Harper, A. K., Fan, R., Majed, R., King, N., Morris, R. T., & Saed, G. M. (2020). Talcum powder induces malignant transformation of human primary normal ovarian epithelial cells but not human primary normal peritoneal fibroblasts. *Gynecologic Oncology*, 159, 140.

¹⁹⁶ Saed, G., Harper, K., & Morris, R. (2021) *Talcum powder induces a malignant transformation in normal ovarian epithelial cells*. Poster presentation: Department of Obstetrics and Gynecology, Wayne State University and Karmanos Cancer Institute, Detroit, MI.

¹⁹⁷ Fletcher, N. M., Harper, A. K., Memaj, I., Fan, R., Morris, R. T., & Saed, G. M. (2019). Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer. *Reproductive Sciences*, 26(12), 1603-1612.

¹⁹⁸ Fletcher, N. M., Harper, A. K., Memaj, I., Fan, R., Morris, R. T., & Saed, G. M. (2019). Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer. *Reproductive Sciences*, 26(12), 1603-1612.

¹⁹⁹ Yudkin, J. S., Lipska, K. J., & Montori, V. M. (2011). The idolatry of the surrogate. *British Medical Journal*, 343.

the fallopian tube or ovary. One might ask why talc particles are proclaimed to inflame the tube and ovary but not the appendix? Why does one not see chronic appendiceal inflammation, as the appendix lies immediately adjacent to the right ovary? Why do we not see an inflamed sigmoid colon, as the sigmoid colon lies immediately adjacent to the left ovary? Why does one not see proctitis or urethritis if the system is open? Why not cystitis? This, combined with the application of the other Bradford Hill criteria, including the lack of strength of association, consistency and dose-response in the epidemiologic literature leads to the conclusion that the genital application of talc is simply not a cause of ovarian cancer. This opinion is stated to a reasonable degree of medical and scientific certainty and is based on a thorough review of the literature, as well as my education, training and 30+ years of experience treating women with gynecologic cancers.

Case Specific Opinions

Ms. Bondurant's perineal use of talcum powder did not cause or contribute to the development of her clear cell ovarian carcinoma. This opinion is based on my training, medical education, 30 years of clinical experience, and review of the peer-reviewed scientific literature, medical records, Plaintiff Profile Form, and relevant deposition testimony. My opinions herein are stated to a reasonable degree of medical certainty.

HISTORY

Ms. Bondurant was a 59 year old, white female,

RISK FACTORS:

Ms. Bondurant's family history was significant for:

[REDACTED]

[REDACTED] . Sia, T.Y. et al published a series of 16 patients with ovarian clear cell carcinoma in 2022 who had undergone treatment with an immune checkpoint inhibitor. One of their patients [REDACTED] had [REDACTED] [REDACTED] It should be noted that genetic testing is a dynamic field with new genetic variants found to be associated with ovarian cancer on a regular basis.

In addition to [REDACTED], Ms. Bondurant had several other well-established risk factors that increased her risk of developing ovarian cancer. Ms. Bondurant had [REDACTED] Dr. Wolf mentioned [REDACTED] as a risk factor in her expert report, but then stated that [REDACTED] A history of [REDACTED] was documented many times in the medical record, in the plaintiff's fact statement as well as in the deposition of the patient's daughter.²⁰²

Moreover, Ms. Bondurant's age at diagnosis (59 years old) and race (Caucasian) are in line with the typical profile of women who develop ovarian cancer.

Ms. Bondurant also had several factors which would have potentially reduced her risk of ovarian cancer, including [REDACTED].

Ms. Bondurant claims to have used Johnson's Baby Powder from 1959-2015, 3-5 times per week, and Shower to Shower from 1970-1980 every day. In defending her case specific opinion regarding talc as the cause of Ms. Bondurant's ovarian cancer, Dr. Wolf used what she referred to as a "differential diagnosis" as her methodology.²⁰³ According to Webster's Dictionary, differential diagnosis is defined as "the distinguishing of a disease or condition from others presenting with similar signs or symptoms."

²⁰⁰ Sia, T.Y., Manning-Giest, B., Gordhandas, S., Rajmohan, M., Marra, A., Liu, Y., Friedman, C., Hollmann, T., Zivanovic, O., Chi, D., Weigelt, B., Konner, J., Zamarin, D. (2022). Treatment of ovarian clear cell carcinoma with immune checkpoint blockade: a case series. *International Journal of Gynecological Cancer*, 32:1017-1024.

²⁰¹ Noli, S., Cipriani, S., Scarfone, G., Villa, A., Grossi, E., Monti, E., & Parazzini, F. (2013). Long term survival of ovarian endometriosis associated clear cell and endometrioid ovarian cancers. *International Journal of Gynecologic Cancer*, 23(2).244-248.

²⁰² Amended Rule 26 Expert Report of Judith Wolf, MD dated November 15, 2023, p.23.

²⁰³ Amended Rule 26 Expert Report of Judith Wolf, MD dated November 15, 2023, pp. 22-23.

Differential diagnosis is not used in medical practice to determine the cause of cancer. Very few cancers have a known cause (lung – tobacco, cervix – HPV, Ovary and Breast -BRCA and other genetic mutations).

[REDACTED] . As discussed more fully above, there simply is no credible scientific evidence that the use of perineal talcum powder increases the risk of ovarian cancer.

CLEAR CELL CARCINOMA OF THE OVARY HAS NO RELATIONSHIP TO TALC USE

Of all the epidemiologic studies that have analyzed the purported risk of Clear Cell Carcinoma of the ovary and talc use, only **one** of them shows a statistically significant increased risk. (see table below)

<u>Author</u>	<u>Year</u>	<u>Study Type</u>	<u>Clear Cell O.R. (C.I)</u>
Cramer²⁰⁴	1999	Meta-Analysis	1.04 (0.67-1.61)*
Wong²⁰⁵	1999	Case Control	1.6 (0.6-4.3)
Mills²⁰⁶	2004	Case Control	0.63 (0.15-2.64)
Merritt²⁰⁷	2008	Case Control	1.08 (0.68-1.72)
Rosenblatt²⁰⁸	2011	Case Control	1.53 (0.91-2.57)*
Terry²⁰⁹	2013	Pooled	1.24 (1.01-1.52)
Cramer²¹⁰	2016	Case Control	1.01 (0.65-1.57)
Berge²¹¹	2018	Meta-Analysis	0.98 (0.72-1.23)
Penninkilampi²¹²	2018	Meta-Analysis	1.02 (0.75-1.39)
Taher²¹³	2019	Meta-Analysis	0.63 (0.15-2.65)
O'Brien²¹⁴	2020	Pooled	1.17 (0.73-1.89)

* Cramer 1999 combined Endometrioid and Clear Cell

* Rosenblatt 2011 combined Endometrioid and Clear Cell

²⁰⁴ Cramer, D. W. (1999). Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. *Obstetrics & Gynecology*, 94(1), 160-161.

²⁰⁵ Wong, C., Hempling, R. E., Piver, M. S., Natarajan, N., & Mettlin, C. J. (1999). Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. *Obstetrics & Gynecology*, 93(3), 372-376.

²⁰⁶ Mills, P. K., Riordan, D. G., Cress, R. D., & Young, H. A. (2004). Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *International Journal of Cancer*, 112(3), 458-464.

²⁰⁷ Merritt, M. A., Green, A. C., Nagle, C. M., Webb, P. M., & Australian Cancer Study (Ovarian Cancer) and Australian Ovarian Cancer Study Group. (2008). Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *International Journal of Cancer*, 122(1), 170-176..

²⁰⁸ Rosenblatt, K. A., Weiss, N. S., Cushing-Haugen, K. L., Wicklund, K. G., & Rossing, M. A. (2011). Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes & Control*, 22(5), 737-742.

²⁰⁹ Terry, K. L., Karageorgi, S., Shvetsov, Y. B., Merritt, M. A., Lurie, G., Thompson, P. J., ... & Australian Ovarian Cancer Study Group. (2013). Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prevention Research*, 6(8), 811-821.

²¹⁰ Cramer, D. W., Vitonis, A. F., Terry, K. L., Welch, W. R., & Titus, L. J. (2016). The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*, 27(3), 334-346

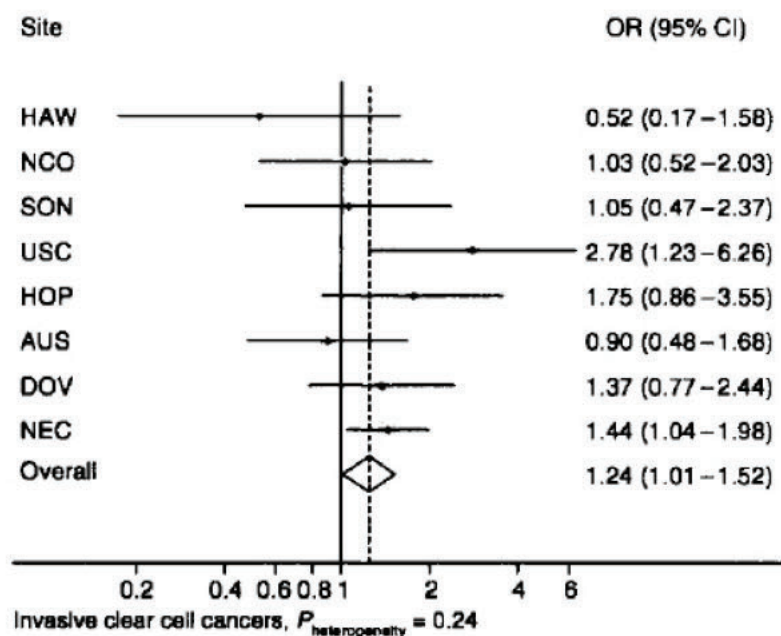
²¹¹ Berge, W., Mundt, K., Luu, H., & Boffetta, P. (2018). Genital use of talc and risk of ovarian cancer: a meta-analysis. *European Journal of Cancer Prevention*, 27(3), 248-257.

²¹² Penninkilampi, R., & Eslick, G. D. (2018). Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. *Epidemiology*, 29(1), 41-49.

²¹³ Taher, M. K., Farhat, N., Karyakina, N. A., Shilnikova, N., Ramoju, S., Gravel, C. A., ... & Krewski, D. (2019). Critical review of the association between perineal use of talc powder and risk of ovarian cancer. *Reproductive Toxicology*, 90, 88-101.

²¹⁴ O'Brien, K. M., Tworoger, S. S., Harris, H. R., Anderson, G. L., Weinberg, C. R., Trabert, B., ... & Wentzensen, N. (2020). Association of powder use in the genital area with risk of ovarian cancer. *JAMA*, 323(1), 49-59.

In a 2013 pooled analysis, Terry et al. demonstrated an O.R. 1.24 (1.01-1.52) when reporting on data from 8 sites analyzing the risk of clear cell carcinoma and talc use.²¹⁵ Of the eight datasets analyzed, only two demonstrated a statistically significant association as shown below.



One of these datasets was from the New England Consortium (NEC). However, 3 years after the Terry (2013) pooled analysis was published, Cramer et al. published data from the NEC, finding no increased risk of clear cell carcinoma in talc users.²¹⁶ Cramer et al. reported on the lack of a relationship to clear cell ovarian cancer in women who reported any use of talcum powder O.R. 1.01 (0.65-1.57). Oddly, there is a discrepancy in the data between Terry (2013) and Cramer (2016). Terry reported 276 clear cell cancer cases from the NEC in 2013, but Cramer reported only 114 clear cell cancer cases from the NEC three years later in 2016. It doesn't make sense that there would be fewer cases of ovarian cases in the NEC after 3 more years of follow up, thereby questioning the validity of the findings in Terry – the only epidemiologic study finding a statistically significant increased risk of clear cell carcinoma in women that used talc.

CONCLUSION

For all of the reasons stated in this expert report, Ms. Bondurant's perineal use of talcum powder did not cause or contribute to the development of her clear cell ovarian cancer. Ms. Bondurant had a clear cell carcinoma of the ovary, which is directly related to her history of endometriosis. Her [REDACTED] also cannot be ruled out as a contributing factor. She also has [REDACTED] indicating a likely genetic cause of her malignancy.

²¹⁵ Terry, K. L., Karageorgi, S., Shvetsov, Y. B., Merritt, M. A., Lurie, G., Thompson, P. J., ... & Australian Ovarian Cancer Study Group. (2013). Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prevention Research*, 6(8), 811-821.

²¹⁶ Cramer, D. W., Vitonis, A. F., Terry, K. L., Welch, W. R., & Titus, L. J. (2016). The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*, 27(3), 334-346.

Exhibit B

MATERIALS RELIED ON AND CONSIDERED BY DR. MICHAEL FINAN

PLAINTIFF PROFILE FORMS

1. Plaintiff Profile Form of Linda Bondurant
2. First Amended Plaintiff Profile Form of Linda Bondurant
3. Second Amended Plaintiff Profile Form of Linda Bondurant

DEPOSITION TRANSCRIPTS

1. 03/18/2021 Deposition Transcript of Jamie Bianca Miller
2. 9/13/2021 Deposition Transcript of Judith Wolf, MD (Vol. 1)
3. 9/14/2021 Deposition Transcript of Judith Wolf, MD (Vol. 2)
4. 1/10/2024 Deposition Transcript of Judith Wolf, MD (Vol. 1)
5. 4/25/2024 Deposition Transcript of Judith Wolf, MD (Vol. 2)

EXPERT REPORTS

1. 08/13/2021 Expert Report of Judith Wolf, MD
2. 11/15/2023 Amended Rule 26 Expert Report of Judith Wolf, MD

MEDICAL RECORDS

1. Acadian Ambulance Service (BondurantL-AASI-00001-00008)
2. Alliance Healthcare Services (BondurantL-AHSI-00001-00018)
3. Ambry Genetics Records (BondurantL-AGC-00001-00053)
4. Aspen Pharmacy (BondurantL-AP-00001-00002)
5. Blue Cross Blue Shield of So. Carolina (BondurantL-BCBSSC-00001-00054)
6. Caris Life Sciences Records (BondurantL-CLS-00001-00138)
7. Casey Williams, MD. Medical Records (BondurantL-WilliamsC-00001-00042)
8. City of New Orleans Emergency Records (BondurantL-CNOEPB-00001-00003)
9. Death Certificate (BondurantL-DeathCert-00001)
10. DePaul Community Health Records (BondurantL-DCHMR-00001-00028; BondurantL-DCHRad-00001-00004)
11. Enclara Pharmacia Inc. (BondurantL-EPI-00001-00003)
12. Flowers Hospital Records (BondurantL-FHMR-00001-00024)
13. Hayward Genetics Center Records (BondurantL-HGCMR-00001-00013)
14. Hayward Genetics Center Tulane Records (BondurantL-HGCTMR-00001-00039; BondurantL-HGCTPB-00001-00002)
15. John Garner, M.D. Medical Records (BondurantL-GarnerJ-00001-00008)
16. MD Anderson Cancer Center (BondurantL-MDAMR-00001-01363; BondurantL-MDAndersonRad-00001-00033; BondurantL-MDAndersonPB-00001-00021; BondurantL-MDARadMAT-00001-00010; BondurantL-MDAPath-00001)
17. Plaintiff Produced Medical Records (LBONDURANT-PL-00001-00044)
18. St Bernard Parish Hospital Records (BondurantL-SBPHMR-00001-00050; BondurantL-SBPHPath-00001-00015; BondurantL-SBPHPB-00001-00014; BondurantL-SBPHRad-00001-00013)
19. Tulane Medical Center Lakeside (BondurantL-TMCLCMR-00001-00066; BondurantL-TMCLCPath-00001-00013; BondurantL-TMCLCPB-00001-00014)
20. Tulane Cancer Center (BondurantL-TCCMR- 00001-01725; BondurantL-TCCRad-00001-00012; TCCPB-00001-00354; TCCPATH-00001-00005)
21. Tulane University (BondurantL-TUMR-00001-01897; BondurantL-TURad-00001-00019)

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22. Tulane University School of Medicine (BondurantL-TUSMMR-00001-02563; BondurantL-TUSMPB-00001-00038; BondurantL-TUSMRad-00001-00012)
23. Troy State University Records (BondurantL-TSU-00001-00009)
24. West Jefferson Medical Center Radiology (BondurantL-WJMCRad-00001-00011)

ADDITIONAL MATERIALS

1. Saed Confidential Documents (SAED_SEPT222021_SUPPL_000001-399)

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